

*Original*PYRAZOLE DERIVATIVES

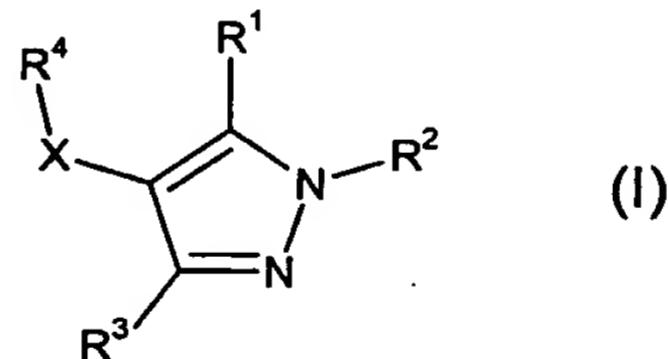
This invention relates to the use of pyrazole derivatives in the manufacture of a reverse transcriptase inhibitor or modulator, to certain novel such pyrazole derivatives and to processes for the preparation of and compositions containing such novel derivatives.

5 The present pyrazole derivatives bind to the enzyme reverse transcriptase and are modulators, especially inhibitors thereof. Reverse transcriptase is implicated in the infectious lifecycle of HIV, and compounds which interfere with the function of this enzyme have shown utility in the treatment of conditions including AIDS. There is a constant need to provide new and better modulators, especially inhibitors, of HIV reverse transcriptase since the virus is
10 able to mutate, becoming resistant to their effects.

The present pyrazole derivatives are useful in the treatment of a variety of disorders including those in which reverse transcriptase is implicated. Disorders of interest include those caused by Human Immunodeficiency Virus (HIV) and genetically related retroviruses, such as Acquired Immune Deficiency Syndrome (AIDS).

15 European Patent Application EP 0 786 455 A1 discloses a class of imidazole compounds which inhibit the growth of HIV. A class of N-phenylpyrazoles which act as reverse transcriptase inhibitors are disclosed in *J. Med. Chem.*, 2000, **43**, 1034. Antiviral activity is ascribed to a class of N-(hydroxyethyl)pyrazole derivatives in US patent number 3,303,200.

20 According to the present invention there is provided the use of a compound of the formula



or a pharmaceutically acceptable salt or solvate thereof, wherein

either (i) R¹ is H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, phenyl, benzyl, halo, -CN, -OR⁷,
25 -OR⁸, -CO₂R⁵, -CONR⁵R⁵, -OCONR⁵R⁵, -NR⁵CO₂R⁷, -NR⁵R⁵, -NR⁵COR⁵,
-NR⁵CO-(C₁-C₆ alkylene)-OR⁵, -NR⁵CONR⁵R⁵, -NR⁵SO₂R⁷ or R⁶, said C₁-C₆ alkyl, C₃-C₇ cycloalkyl, phenyl and benzyl being optionally substituted by halo, -CN, -OR⁵, -OR⁸, -CO₂R⁵, -CONR⁵R⁵, -OCONR⁵R⁵, -NR⁵CO₂R⁷, -NR⁵R⁵, -NR⁸R⁹,
-NR⁵COR⁵, -NR⁵COR⁶, -NR⁵COR⁸, -SO₂NR⁵R⁵, -NR⁵CONR⁵R⁵, -NR⁵SO₂R⁷ or R⁶,
30 and
R² is H or -Y-Z,

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or, (ii) R¹ and R², when taken together, represent unbranched C₃-C₄ alkylene, optionally wherein one methylene group of said C₃-C₄ alkylene is replaced by an oxygen atom or a nitrogen atom, said nitrogen atom being optionally substituted by R⁵ or R⁸;

Y is a direct bond or C₁-C₃ alkylene;

5 Z is R¹⁰ or, where Y is C₁-C₃ alkylene, Z is -NR⁵COR¹⁰, -NR⁵CONR⁵R¹⁰, -NR⁵CONR⁵COR¹⁰ or -NR⁵SO₂R¹⁰;

R³ is H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, phenyl, benzyl, -CN, halo, -OR⁷, -CO₂R⁵, -CONR⁵R⁵, -OCONR⁵R⁵, -NR⁵CO₂R⁷, -NR⁵R⁵, -NR⁵COR⁵, -NR⁵CONR⁵R⁵, -NR⁵SO₂R⁷ or R⁶, said C₁-C₆ alkyl, C₃-C₇ cycloalkyl, phenyl and benzyl being

10 optionally substituted by halo, -CN, -OR⁵, -CO₂R⁵, -CONR⁵R⁵, -OCONR⁵R⁵, -NR⁵CO₂R⁷, -NR⁵R⁵, -NR⁵COR⁵, -SO₂NR⁵R⁵, -NR⁵CONR⁵R⁵, -NR⁵SO₂R⁷ or R⁶;

R⁴ is phenyl or pyridyl, each being optionally substituted by R⁶, halo, -CN, C₁-C₆ alkyl, fluoro-(C₁-C₆)-alkyl, C₃-C₇ cycloalkyl or C₁-C₆ alkoxy;

each R⁵ is independently either H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, fluoro-(C₁-C₆)-alkyl, 15 phenyl or benzyl, or, when two such groups are attached to the same nitrogen atom, those two groups taken together with the nitrogen atom to which they are attached represent azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl or morpholinyl, said azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl and morpholinyl being optionally substituted by C₁-C₆ alkyl or C₃-C₇ cycloalkyl and said piperazinyl and homopiperazinyl being optionally substituted on the nitrogen atom not taken together with the two R⁵ groups to form the ring by -COR⁷ or -SO₂R⁷;

20 R⁶ is a four to six-membered, aromatic, partially unsaturated or saturated heterocyclic group containing (i) from 1 to 4 nitrogen heteroatom(s) or (ii) 1 or 2 nitrogen heteroatom(s) and 1 oxygen or 1 sulphur heteroatom or (iii) 1 or 2 oxygen or sulphur heteroatom(s), said heterocyclic group being optionally substituted by -OR⁵, -NR⁵R⁵, -CN, oxo, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, -COR⁷ or halo;

R⁷ is C₁-C₆ alkyl, C₃-C₇ cycloalkyl, fluoro-(C₁-C₆)-alkyl, phenyl or benzyl;

R⁸ is C₁-C₆ alkyl substituted by phenyl, phenoxy, pyridyl or pyrimidinyl, said phenyl, phenoxy, pyridyl and pyrimidinyl being optionally substituted by halo,

30 -CN, -CONR⁵R⁵, -SO₂NR⁵R⁵, -NR⁵SO₂R⁷, -NR⁵R⁵, -(C₁-C₆ alkylene)-NR⁵R⁵, C₁-C₆ alkyl, fluoro-(C₁-C₆)-alkyl, C₃-C₇ cycloalkyl or C₁-C₆ alkoxy;

R⁹ is H, C₁-C₆ alkyl or C₃-C₇ cycloalkyl, said C₁-C₆ alkyl and C₃-C₇ cycloalkyl being optionally substituted by -OR⁵, -NR⁵R⁵, -NR⁵COR⁵, -CONR⁵R⁵ or R⁶;

35 R¹⁰ is C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₇ cycloalkyl, phenyl, benzyl or C-linked R⁶, said C₁-C₆ alkyl, C₃-C₇ cycloalkyl, phenyl and benzyl being optionally substituted by halo, -OR⁵, -OR¹², -CN, -CO₂R⁷, -CONR⁵R⁵, -OCONR⁵R⁵, -C(=NR⁵)NR⁵OR⁵, -CONR⁵NR⁵R⁵, -OCONR⁵CO₂R⁷, -NR⁵R⁵, -NR⁵R¹², -NR⁵COR⁵,

-NR⁵CO₂R⁷, -NR⁵CONR⁵R⁵, -NR⁵COCONR⁵R⁵, -NR⁵SO₂R⁷, -SO₂NR⁵R⁵ or R⁶;

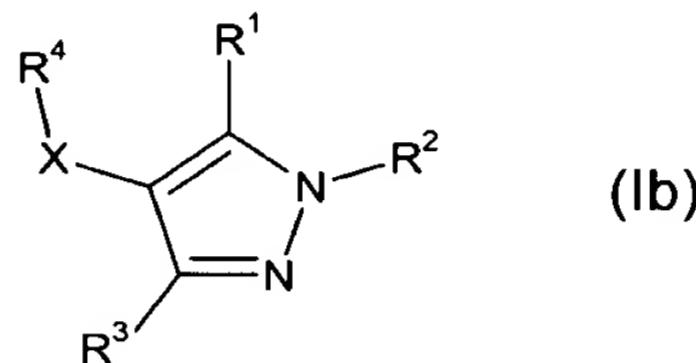
X is -CH₂-, -CHR¹¹-, -CO-, -S-, -SO- or -SO₂-;

R¹¹ is C₁-C₆ alkyl, C₃-C₇ cycloalkyl, fluoro-(C₁-C₆)-alkyl or C₁-C₆ alkoxy; and

R¹² is C₁-C₆ alkyl substituted by R⁶, -OR⁵, -CONR⁵R⁵, -NR⁵COR⁵ or -NR⁵R⁵;

5 in the manufacture of (a) a reverse transcriptase inhibitor or modulator or (b) a medicament for the treatment of a human immunodeficiency viral (HIV), or genetically related retroviral, infection or a resulting acquired immunodeficiency syndrome (AIDS).

The present invention also provides a novel compound of the formula



10 or a pharmaceutically acceptable salt or solvate thereof, wherein

either (i) R¹ is H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, phenyl, benzyl, halo, -CN, -OR⁷, -CO₂R⁵, -CONR⁵R⁵, -OCONR⁵R⁵, -NR⁵CO₂R⁷, -NR⁵R⁵, -NR⁵COR⁵, -NR⁵CO-(C₁-C₆ alkylene)-OR⁵, -NR⁵CONR⁵R⁵, -NR⁵SO₂R⁷ or R⁶, said C₁-C₆ alkyl, C₃-C₇ cycloalkyl, phenyl and benzyl being optionally substituted by halo, -CN, -OR⁵, -OR⁸, -CO₂R⁵, -CONR⁵R⁵, -OCONR⁵R⁵, -NR⁵CO₂R⁷, -NR⁵R⁵, -NR⁸R⁹, -NR⁵COR⁵, -NR⁵COR⁶, -NR⁵COR⁸, -SO₂NR⁵R⁵, -NR⁵CONR⁵R⁵, -NR⁵SO₂R⁷ or R⁶ and

R² is -Y-Z,

or, R¹ and R², when taken together, represent unbranched C₃-C₄ alkylene, optionally wherein one methylene group of said C₃-C₄ alkylene is replaced by an oxygen atom or a 20 nitrogen atom, said nitrogen atom being optionally substituted by R⁵ or R⁸,

and R³ is H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, phenyl, benzyl, -CN, halo, -OR⁷, -CO₂R⁵, -CONR⁵R⁵, -OCONR⁵R⁵, -NR⁵CO₂R⁷, -NR⁵R⁵, -NR⁵COR⁵, -NR⁵CONR⁵R⁵, -NR⁵SO₂R⁷ or R⁶, said C₁-C₆ alkyl, C₃-C₇ cycloalkyl, phenyl and benzyl being optionally substituted by halo, -CN, -OR⁵, -CO₂R⁵, -CONR⁵R⁵, -OCONR⁵R⁵, -NR⁵CO₂R⁷, -NR⁵R⁵, -NR⁵COR⁵, -SO₂NR⁵R⁵, -NR⁵CONR⁵R⁵, -NR⁵SO₂R⁷ or R⁶,

or (ii) R¹ and R³ are each independently C₁-C₆ alkyl, C₃-C₇ cycloalkyl or halo-(C₁-C₆ alkyl), and R² is H,

provided that

(a) for definition (i), R¹ and R³ are not both H,

30 (b) for definition (i), R¹ and R³ are not both optionally substituted phenyl, as defined therein,

(c) for definition (i), when R¹ and R³ are both methyl, R² is not phenyl or methyl, and

(d) for definition (ii), R¹ and R³ are not both methyl;
Y is a direct bond or C₁-C₃ alkylene;
Z is R¹⁰ or, where Y is C₁-C₃ alkylene, Z is -NR⁵COR¹⁰, -NR⁵CONR⁵R¹⁰,
-NR⁵CONR⁵COR¹⁰ or -NR⁵SO₂R¹⁰;

5 R⁴ is phenyl or pyridyl, each substituted by at least one substituent selected from
halo, -CN, C₁-C₆ alkyl, fluoro-(C₁-C₆)-alkyl, C₃-C₇ cycloalkyl and C₁-C₆ alkoxy;
each R⁵ is independently either H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, fluoro-(C₁-C₆)-alkyl,
phenyl or benzyl, or, when two such groups are attached to the same nitrogen atom, those
two groups taken together with the nitrogen atom to which they are attached represent

10 azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl or
morpholinyl, said azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl,
homopiperazinyl and morpholinyl being optionally substituted by C₁-C₆ alkyl or C₃-C₇
cycloalkyl and said piperazinyl and homopiperazinyl being optionally substituted on the
nitrogen atom not taken together with the two R⁵ groups to form the ring by -COR⁷ or -SO₂R⁷;

15 R⁶ is a four to six-membered, aromatic, partially unsaturated or saturated heterocyclic
group containing (i) from 1 to 4 nitrogen heteroatom(s) or (ii) 1 or 2 nitrogen heteroatom(s)
and 1 oxygen or 1 sulphur heteroatom or (iii) 1 or 2 oxygen or sulphur heteroatom(s), said
heterocyclic group being optionally substituted by -OR⁵, -NR⁵R⁵, -CN, oxo, C₁-C₆ alkyl, C₃-C₇
cycloalkyl, -COR⁷ or halo;

20 R⁷ is C₁-C₆ alkyl, C₃-C₇ cycloalkyl, fluoro-(C₁-C₆)-alkyl, phenyl or benzyl;
R⁸ is C₁-C₆ alkyl substituted by phenyl, pyridyl or pyrimidinyl, said phenyl, pyridyl and
pyrimidinyl being optionally substituted by halo, -CN, -CONR⁵R⁵, -SO₂NR⁵R⁵,
-NR⁵SO₂R⁷, -NR⁵R⁵, -(C₁-C₆ alkylene)-NR⁵R⁵, C₁-C₆ alkyl, fluoro-(C₁-C₆)-alkyl, C₃-C₇
cycloalkyl or C₁-C₆ alkoxy;

25 R⁹ is H, C₁-C₆ alkyl or C₃-C₇ cycloalkyl, said C₁-C₆ alkyl and C₃-C₇ cycloalkyl being
optionally substituted by -OR⁵, -NR⁵R⁵, -NR⁵COR⁵, -CONR⁵R⁵ or R⁶;
R¹⁰ is (a) benzyl or C-linked R⁶, said benzyl being optionally substituted by halo,
-OR⁵, -OR¹², -CN, -CO₂R⁷, -CONR⁵R⁵, -OCONR⁵R⁵, -C(=NR⁵)NR⁵OR⁵, -CONR⁵NR⁵R⁵,
-CONR⁵CO₂R⁷, -NR⁵R⁵, -NR⁵R¹², -NR⁵COR⁵, -NR⁵CO₂R⁷, -NR⁵CONR⁵R⁵, -NR⁵COCONR⁵R⁵,
30 -NR⁵SO₂R⁷, -SO₂NR⁵R⁵ or R⁶, or (b) when R¹ and R³ are each independently C₁-C₆ alkyl,
C₃-C₇ cycloalkyl or halo-(C₁-C₆ alkyl), R¹⁰ is phenyl, C₁-C₆ alkyl or C₃-C₇ cycloalkyl each being
optionally substituted by halo, -OR⁵, -OR¹², -CN, -CO₂R⁷, -CONR⁵R⁵, -OCONR⁵R⁵,
-C(=NR⁵)NR⁵OR⁵, -CONR⁵NR⁵R⁵, -OCONR⁵CO₂R⁷, -NR⁵R⁵, -NR⁵R¹², -NR⁵COR⁵,
-NR⁵CO₂R⁷, -NR⁵CONR⁵R⁵, -NR⁵COCONR⁵R⁵, -NR⁵SO₂R⁷, -SO₂NR⁵R⁵ or R⁶;

35 X is -CH₂-, -CHR¹¹-, -CO-, -S-, -SO- or -SO₂;-
R¹¹ is C₁-C₆ alkyl, C₃-C₇ cycloalkyl, fluoro-(C₁-C₆)-alkyl or C₁-C₆ alkoxy; and
R¹² is C₁-C₆ alkyl substituted by R⁶, -OR⁵, -CONR⁵R⁵, -NR⁵COR⁵ or -NR⁵R⁵.

In the above definitions, halo means fluoro, chloro, bromo or iodo. Unless otherwise stated, alkyl, alkenyl, alkynyl, alkylene and alkoxy groups containing the requisite number of carbon atoms can be unbranched or branched chain. Examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. Examples of alkenyl include ethenyl, 5 propen-1-yl, propen-2-yl, propen-3-yl, 1-buten-1-yl, 1-buten-2-yl, 1-buten-3-yl, 1-buten-4-yl, 2-buten-1-yl, 2-buten-2-yl, 2-methylpropen-1-yl or 2-methylpropen-3-yl. Examples of alkynyl include ethynyl, propyn-1-yl, propyn-3-yl, 1-butyn-1-yl, 1-butyn-3-yl, 1-butyn-4-yl, 2-butyn-1-yl. Examples of alkylene include methylene, 1,1-ethylene, 1,2-ethylene, 1,1-propylene, 1,2-propylene, 2,2-propylene and 1,3-propylene. Examples of alkoxy include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. 'C-linked' used in the definition of R¹⁰ means that the R¹⁰ substituent is attached through a ring carbon atom. Where R¹ and R² are taken together, they form, along with the nitrogen atom and the carbon atom of the pyrazole ring to which they are attached, a 5- or 6-membered ring.

15 The pharmaceutically acceptable salts of the compounds of the formula (I) and the compounds of the formula (Ib) include the acid addition and the base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, 20 gluconate, succinate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, para-toluenesulphonate and pamoate salts.

Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts.

For a review on suitable salts see Berge *et al*, *J. Pharm. Sci.*, **66**, 1-19, 1977.

25 The pharmaceutically acceptable solvates of the compounds of the formula (I) and the compounds of the formula (Ib), and the salts thereof, include the hydrates thereof.

Also included within the present scope of the compounds of the formula (I) and the compounds of the formula (Ib) are polymorphs thereof.

A compound of the formula (I) or a compound of the formula (Ib) may contain one or 30 more asymmetric carbon atoms and therefore exist in two or more stereoisomeric forms. The present invention includes the individual stereoisomers of the compounds of the formula (I) and the compounds of the formula (Ib) together with, where appropriate, the individual tautomers thereof, and mixtures thereof.

Separation of diastereoisomers may be achieved by conventional techniques, e.g. by 35 fractional crystallisation, chromatography or high performance liquid chromatography (HPLC) of a stereoisomeric mixture of a compound of the formula (I) or a compound of the formula (Ib) or a suitable salt or derivative thereof. An individual enantiomer of a compound of the

formula (I) or a compound of the formula (Ib) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by HPLC of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base,
5 as appropriate.

Preferred individual compounds according to the invention include the Examples below.

Particularly preferred individual compounds according to the invention include
2-{4-[(3,5-dichlorophenyl)sulfanyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}ethanol;
10 2-[4-[(3,5-dichlorophenyl)sulfanyl]-3-ethyl-5-(hydroxymethyl)-1*H*-pyrazol-1-yl]ethanol;
and
2-{4-[(3,5-dichlorophenyl)sulfanyl]-3,5-diethyl-1*H*-pyrazol-1-yl}ethanol.

The following preferred features of the invention relate both to compounds of the formula (I) and compounds of the formula (Ib).

15 Preferably, R¹ is C₁-C₆ alkyl, -OR⁷, -CO₂R⁵, -NR⁵CO₂R⁷, -NR⁵R⁵, -NR⁵CO-(C₁-C₆ alkylene)-OR⁵ or R⁶, said C₁-C₆ alkyl being optionally substituted by halo, -CN, -OR⁵, -OR⁸, -CO₂R⁵, -CONR⁵R⁵, -OCONR⁵R⁵, -NR⁵CO₂R⁷, -NR⁵R⁵, -NR⁸R⁹, -NR⁵COR⁵, -NR⁵COR⁶, -NR⁵COR⁸, -SO₂NR⁵R⁵, -NR⁵CONR⁵R⁵, -NR⁵SO₂R⁷ or R⁶.

20 Preferably, R¹ is C₁-C₆ alkyl, -OR⁷, -CO₂R⁵, -NR⁵CO₂R⁷, -NR⁵R⁵, -NR⁵CO-(C₁-C₆ alkylene)-OR⁵ or R⁶, said C₁-C₆ alkyl being optionally substituted by halo or -OR⁵.

Preferably, R¹ is C₁-C₃ alkyl, -OCH₃, -CO₂(C₁-C₂ alkyl), -NHCO₂(C₁-C₂ alkyl), -NH₂, -N(CH₃)₂, -NHCOCH₂OCH₃ or furanyl, said C₁-C₃ alkyl being optionally substituted by fluoro or -OH.

25 Preferably, R¹ is methyl, ethyl, prop-2-yl, hydroxymethyl, trifluoromethyl, -OCH₃, -CO₂CH₂CH₃, -NHCO₂CH₂CH₃, -NH₂, -N(CH₃)₂, -NHCOCH₂OCH₃ or furan-2-yl.

Preferably, R¹ is ethyl.

Preferably, R¹ is methyl, ethyl, trifluoromethyl or -CH₂NHCH₂(4-cyanophenyl).

30 Preferably, R² is H, C₁-C₆ alkyl, -(C₁-C₃ alkylene)-NR⁵CO-(C₁-C₆ alkyl), -(C₁-C₃ alkylene)-NR⁵CONR⁵-(C₁-C₆ alkyl), -(C₁-C₃ alkylene)-NR⁵CONR⁵CO-(phenyl), -(C₁-C₃ alkylene)-NR⁵SO₂(C-linked R⁶), -(C₁-C₃ alkylene)-NR⁵CO(C-linked R⁶), -(C₁-C₃ alkylene)-NR⁵CO-(phenyl), each C₁-C₆ alkyl and phenyl being optionally substituted by halo, -OR⁵, -OR¹², -CN, -CO₂R⁷, -CONR⁵R⁵, -OCONR⁵R⁵, -C(=NR⁵)NR⁵OR⁵, -CONR⁵NR⁵R⁵, -OCONR⁵CO₂R⁷, -NR⁵R⁵, -NR⁵R¹², -NR⁵COR⁵, -NR⁵CO₂R⁷, -NR⁵CONR⁵R⁵, -NR⁵COCONR⁵R⁵, -NR⁵SO₂R⁷, -SO₂NR⁵R⁵ or R⁶.

35 Preferably, R² is H, C₁-C₆ alkyl, -(C₁-C₃ alkylene)-NR⁵CO-(C₁-C₆ alkyl), -(C₁-C₃ alkylene)-NR⁵CONR⁵-(C₁-C₆ alkyl), -(C₁-C₃ alkylene)-NR⁵CONR⁵CO-(phenyl),

-(C₁-C₃ alkylene)-NR⁵SO₂R⁶, -(C₁-C₃ alkylene)-NR⁵COR⁶, -(C₁-C₃ alkylene)-NR⁵CO-(phenyl), each C₁-C₆ alkyl and phenyl being optionally substituted by halo, -OR⁵, -CN, -CO₂R⁷, -CONR⁵R⁵, -OCONR⁵R⁵, -OCONR⁵CO₂R⁷, -NR⁵R⁵, -NR⁵CONR⁵R⁵, -NR⁵COCONR⁵R⁵ or R⁶.

5 Preferably, R² is H, C₁-C₃ alkyl, -(C₁-C₂ alkylene)-NHCO-(C₁-C₃ alkyl), -(C₁-C₂ alkylene)-NHCONH-(C₁-C₃ alkyl), -(C₁-C₂ alkylene)-NHCONHCO-(phenyl), -(C₁-C₂ alkylene)-NHSO₂R⁶, -(C₁-C₂ alkylene)-NHCOR⁶, -(C₁-C₂ alkylene)-NHCO-(phenyl), each C₁-C₃ alkyl and phenyl being optionally substituted by fluoro, -OH, -O(C₁-C₆ alkyl), -CN, -CO₂(C₁-C₆ alkyl), -CONH₂, -OCONH₂, -OCONHCO₂Ph, -NH₂, -N(C₁-C₆ alkyl)₂, -NHCONH₂, 10 -NHCOCONH₂ or R⁶.

Preferably, R² is H, -CH₂OH, -CH₂CH₂OH, -CH₂CH₂CH₂OH, -CH₂OCONH₂, -CH₂CH₂OCONH₂, -CH₂OCONHCO₂Ph, -CH₂CO₂CH₂CH₃, -CH₂CH₂CO₂CH₂CH₃, -CH₂CH₂CONH₂, -CH₂CH₂NH₂, -CH₂CH₂CH₂NH₂, -CH₂CH₂NHCOCH₂F₂, -CH₂CH₂NHCOCH₂CN, -CH₂CH₂NHCOCH₂OCH₃, 15 -CH₂CH₂NHCOCH₂NHCONH₂, -CH₂CH₂NHCOCH₂OH, -CH₂CH₂NHCOCH₂OCH₂CH₃, -CH₂CH₂NHCONHCOPh, -CH₂CH₂NHCONHCO(2,6-difluorophenyl), -CH₂CH₂NHSO₂(2,4-dihydroxypyrimidin-5-yl), -CH₂CH₂NHSO₂(1-methylimidazol-4-yl), -CH₂CH₂NHCO(tetrahydrofuran-2-yl), 20 -CH₂CH₂NHCO(1,5-dimethylpyrazol-3-yl), -CH₂CH₂NHCOCH₂(tetrazol-1-yl), -CH₂CH₂NHCOPh, -CH₂CH₂NHCO(pyridin-2-yl), -CH₂CH₂NHCO(pyrimidin-2-yl), -CH₂CH₂NHCO(2-fluorophenyl), -CH₂CH₂NHCO(3-hydroxyphenyl), -CH₂CH₂NHCO(3-hydroxypyridazin-6-yl), -CH₂CH₂NHCO(2-hydroxypyridin-6-yl), -CH₂CH₂NHCO(2-oxo-2H-pyran-5-yl) or -CH₂CH₂NHCO(1,2,3-thiadiazol-4-yl).

25 Preferably, R² is H, methyl, -CH₂CH₂OH, -CH₂CH₂CH₂OH, -CH₂CH₂NH₂, -CH₂CH₂CH₂NH₂, -CH₂CH₂NH₂, -CH₂CN, -CH₂CH₂OCH₃, -CH₂CONH₂, -CH₂CH₂NHCOCH₂OCH₃ or azetidin-3-yl.

Preferably, R² is -CH₂CH₂OH, -CH₂CH₂NH₂, -CH₂CN or azetidin-3-yl.

30 Preferably, R³ is C₁-C₆ alkyl, -CO₂R⁵, -CONR⁵R⁵, -NR⁵CO₂R⁷ or -NR⁵R⁵, said C₁-C₆ alkyl being optionally substituted by halo, -CN, -OR⁵, -CO₂R⁵, -CONR⁵R⁵, -OCONR⁵R⁵, -NR⁵CO₂R⁷, -NR⁵R⁵, -NR⁵COR⁵, -SO₂NR⁵R⁵, -NR⁵CONR⁵R⁵, -NR⁵SO₂R⁷ or R⁶.

Preferably, R³ is C₁-C₆ alkyl, -CO₂R⁵, -CONR⁵R⁵, -NR⁵CO₂R⁵ or -NR⁵R⁵, said C₁-C₆ alkyl being optionally substituted by halo, -CN or -OR⁵.

35 Preferably, R³ is C₁-C₃ alkyl, -CO₂(C₁-C₂ alkyl), -CONH₂, -NHCO₂(C₁-C₄ alkyl), -N(CH₃)₂ or -NH₂, said C₁-C₃ alkyl being optionally substituted by halo, -CN or -OH.

Preferably, R³ is methyl, ethyl, prop-2-yl, hydroxymethyl, cyanomethyl, trifluoromethyl, -CO₂CH₂CH₃, -CONH₂, -NHCO₂C(CH₃)₃, -N(CH₃)₂ or -NH₂.

Preferably, R³ is methyl, ethyl, prop-2-yl or trifluoromethyl.

Preferably, R³ is ethyl.

Preferably, X is -CH₂-, -CHR¹¹-, -CO-, -S- or -SO₂-.

Preferably, X is -CH₂-, -CH(OCH₃)-, -CO-, -S- or -SO₂-.

5 Preferably, X is -CH₂- or -S-.

Preferably, R⁶ is azetidinyl, tetrahydropyrrolyl, piperidinyl, azepinyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, oxepinyl, morphoninyl, piperazinyl, diazepinyl, pyrrolyl, furanyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyranyl, pyridazinyl, pyrimidinyl or pyrazinyl each 10 being optionally substituted by -OR⁵, -NR⁵R⁵, -CN, oxo, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, -COR⁷ or halo.

Preferably, R⁶ is furan-2-yl, 2,4-dihydroxypyrimidinyl, 1-methylimidazolyl, tetrahydrofuranyl, 1,5-dimethylpyrazolyl, tetrazolyl, pyridinyl, pyrimidinyl, 3-hydroxypyridazinyl, 2-hydroxypyridinyl, 2-oxo-2H-pyranyl or 1,2,3-thiadiazolyl.

15 Preferably, R⁶ is 2,4-dihydroxypyrimidinyl, 1-methylimidazolyl, tetrahydrofuranyl, 1,5-dimethylpyrazolyl, tetrazolyl, pyridinyl, pyrimidinyl, 3-hydroxypyridazinyl, 2-hydroxypyridinyl, 2-oxo-2H-pyranyl or 1,2,3-thiadiazolyl.

20 Preferably, R¹⁰ is C₁-C₆ alkyl, phenyl, or C-linked R⁶, said C₁-C₆ alkyl and phenyl being optionally substituted by halo, -OR⁵, -OR¹², -CN, -CO₂R⁷, -CONR⁵R⁵, -OCONR⁵R⁵, -C(=NR⁵)NR⁵OR⁵, -CONR⁵NR⁵R⁵, -OCONR⁵CO₂R⁷, -NR⁵R⁵, -NR⁵R¹², -NR⁵COR⁵, -NR⁵CO₂R⁷, -NR⁵CONR⁵R⁵, -NR⁵COCONR⁵R⁵, -NR⁵SO₂R⁷, -SO₂NR⁵R⁵ or R⁶.

25 Preferably, R¹⁰ is C₁-C₆ alkyl, phenyl, or C-linked R⁶, said C₁-C₆ alkyl and phenyl being optionally substituted by halo, -OR⁵, -CN, -CO₂R⁷, -CONR⁵R⁵, -OCONR⁵R⁵, -OCONR⁵CO₂R⁷, -NR⁵R⁵, -NR⁵CONR⁵R⁵, -NR⁵COCONR⁵R⁵ or R⁶.

30 Preferably, R¹⁰ is C₁-C₃ alkyl, phenyl, or R⁶, said C₁-C₃ alkyl and phenyl being optionally substituted by fluoro, -OH, -O(C₁-C₆ alkyl), -CN, -CO₂(C₁-C₆ alkyl), -CONH₂, -OCONH₂, -OCONHCO₂Ph, -NH₂, -N(C₁-C₆ alkyl)₂, -NHCONH₂, -NHCOCOCONH₂ or R⁶.

35 Preferably, R¹⁰ is -CH₂OH, -CH₂CH₂OH, -CH₂CH₂CH₂OH, -CH₂OCONH₂, -H₂CH₂OCONH₂, -CH₂OCONHCO₂Ph, -CH₂CO₂CH₂CH₃, -CH₂CH₂CO₂CH₃, -CH₂CH₂CO₂CH₂CH₃, -CH₂CH₂CONH₂, -CH₂CH₂NH₂, -CH₂CH₂CH₂NH₂, -CHF₂, -CH₂CN, -₂N(CH₃)₂, -CH₂OCH₃, -CH₂OH, -CH₂OCH₂CH₃, CH₂NHCONH₂, -CH₂CH₂NHCOCOCONH₂, -CH₂CH₂CH₃, phenyl, 2,6-difluorophenyl, 2,4-dihydroxypyrimidin-5-yl, 1-methylimidazol-4-yl, tetrahydrofuran-2-yl, 1,5-dimethylpyrazol-3-yl, -CH₂(tetrazol-1-yl), pyridin-2-yl, pyrimidin-2-yl, 2-fluorophenyl, 3-hydroxyphenyl, 3-hydroxypyridazin-6-yl, 2-hydroxypyridin-6-yl, 2-oxo-2H-pyran-5-yl or 1,2,3-thiadiazol-4-yl.

Preferably, R¹⁰ is methyl, -CH₂CH₂OH, -CH₂CH₂CH₂OH, -CH₂CH₂NH₂,

-CH₂CH₂CH₂NH₂, -CH₂CN, -CH₂CH₂OCH₃, -CH₂CONH₂, -CH₂CH₂NHCOCH₂OCH₃ or azetidin-3-yl.

The following preferred features of the invention relate to compounds of the formula (I).

5 Preferably, R⁴ is phenyl optionally substituted by R⁶, halo, -CN, C₁-C₆ alkyl, fluoro-(C₁-C₆)-alkyl, C₃-C₇ cycloalkyl or C₁-C₆ alkoxy.

Preferably, R⁴ is phenyl substituted by halo, -CN or C₁-C₃ alkyl.

Preferably, R⁴ is phenyl substituted by fluoro, chloro, bromo, -CN, or methyl.

10 Preferably, R⁴ is 3-chlorophenyl, 4-chlorophenyl, 3-fluorophenyl, 3,5-dichlorophenyl, 2,6-difluorophenyl, 3,5-difluorophenyl, 3,5-dicyanophenyl, 3,5-dibromophenyl or 3,5-dimethylphenyl.

Preferably, R⁴ is (i) phenyl substituted at the 3 position by fluoro, chloro, methyl or cyano or (ii) phenyl substituted at the 3 and 5 positions by two substituents independently chosen from fluoro, chloro, methyl and cyano.

15 The following preferred features of the invention relate to compounds of the formula (Ib).

Preferably, R⁴ is phenyl substituted by at least one substituent selected from halo, -CN, C₁-C₆ alkyl, fluoro-(C₁-C₆)-alkyl, C₃-C₇ cycloalkyl and C₁-C₆ alkoxy.

20 Preferably, R⁴ is phenyl substituted by at least one substituent selected from halo, -CN and C₁-C₃ alkyl.

Preferably, R⁴ is phenyl substituted by at least one substituent selected from fluoro, chloro, bromo, -CN and methyl.

25 Preferably, R⁴ is 3-chlorophenyl, 4-chlorophenyl, 3-fluorophenyl, 3,5-dichlorophenyl, 2,6-difluorophenyl, 3,5-difluorophenyl, 3,5-dicyanophenyl, 3,5-dibromophenyl or 3,5-dimethylphenyl.

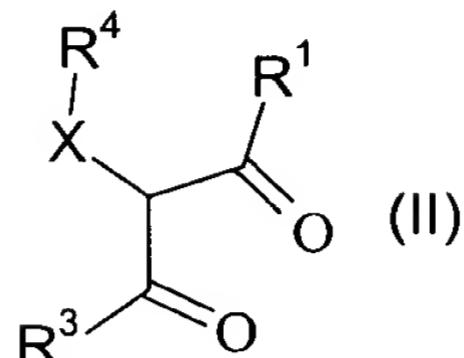
Preferably, R⁴ is (i) phenyl substituted at the 3 position by fluoro, chloro, methyl or cyano or (ii) phenyl substituted at the 3 and 5 positions by two substituents independently chosen from fluoro, chloro, methyl and cyano.

30 All of the compounds of the formula (I) and the compounds of the formula (Ib) can be prepared by conventional routes such as by the procedures described in the general methods presented below or by the specific methods described in the Examples section, or by similar methods thereto. The present invention also encompasses any one or more of these processes for preparing the compounds of formula (Ib).

In the following general methods, R¹, R², R³, R⁴ and X are as previously defined for a compound of the formula (Ib) or a compound of the formula (I) unless otherwise stated.

Compounds of the formula (Ib) and compounds of the formula (I) in which R¹ and R³ are each either H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, phenyl, benzyl, -CO₂R⁵, -CONR⁵R⁵, or C-

linked R⁶, optionally substituted where allowed, may be prepared by the reaction of a compound of the formula

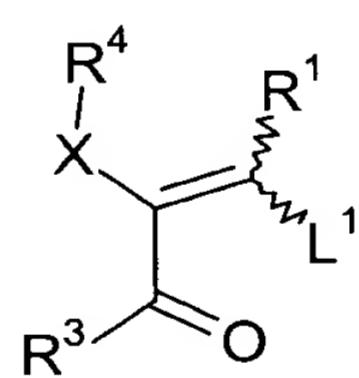


with a compound of the formula

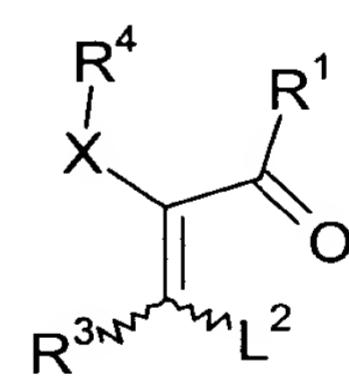
$$5 \quad \text{H}_2\text{NNHR}^2 \text{ (III),}$$

or a salt or hydrate thereof, optionally in the presence of an acid or a base, the base preferably being a tertiary amine base such as triethylamine and the acid preferably being acetic acid. In a typical procedure, a solution of the compound of the formula (II) in a suitable solvent, such as ethanol, is treated with the compound of the formula (III), or the salt or hydrate thereof, and, if used, the appropriate acid or base, at a temperature of from room temperature to the reflux temperature of the solvent. In a preferred procedure, the reaction mixture is heated under reflux.

Functional equivalents of compounds of the formula (II) may also be used in this reaction. These include compounds of the formula (IV) or (V), in which L¹ and L², respectively, are each suitable leaving groups, preferably -N(C₁-C₆ alkyl)₂, most preferably -N(CH₃)₂.



(IV)

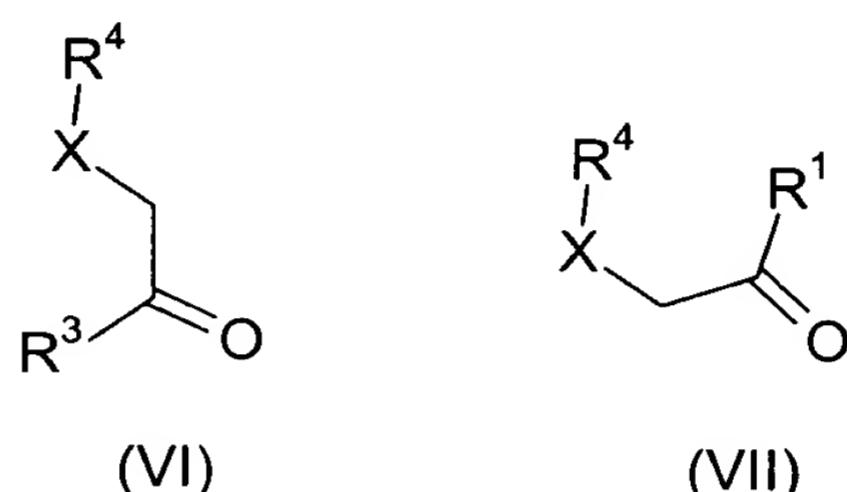


(V)

Thus, a compound of the formula (Ib) or a compound of the formula (I) may be prepared by the condensation of a compound of the formula (IV) or (V) with a compound of the formula (III), or a salt or hydrate thereof, optionally in the presence of an acid or a base, the base preferably being a tertiary amine base such as triethylamine and the acid preferably being acetic acid. In a typical procedure, a solution of the compound of the formula (IV) or (V) in a suitable solvent, such as acetic acid, is treated with the compound of the formula (III), or the salt or hydrate thereof, and, if used, the appropriate acid or base, at a temperature of from room temperature to the reflux temperature of the solvent. In a preferred procedure, the reaction mixture is heated under reflux. Compounds of the formula (IV) or (V) are particularly suitable for the synthesis of compounds of the formula (Ib) or compounds of the formula (I) in which R¹ or R³, respectively, is H.

Compounds of the formula (IV) in which R¹ is H and L¹ is dimethylamino may be prepared by the reaction of a compound of the formula (VI) with dimethylformamide dimethylacetal at an elevated temperature, preferably at about 100°C. Compounds of the formula (V) in which R³ is H and L² is dimethylamino may be prepared by the reaction of a compound of the formula (VII) under the same conditions. Other compounds of the formula (IV) or (V) in which L¹ or L² is dimethylamino may be prepared analogously.

Compounds of the formula (VI) are either commercially available or may be prepared



10 by methods well known in the art. For example, where X is S, compounds of the formula (VI) may be prepared by the reaction of a compound of the formula



with a compound of the formula



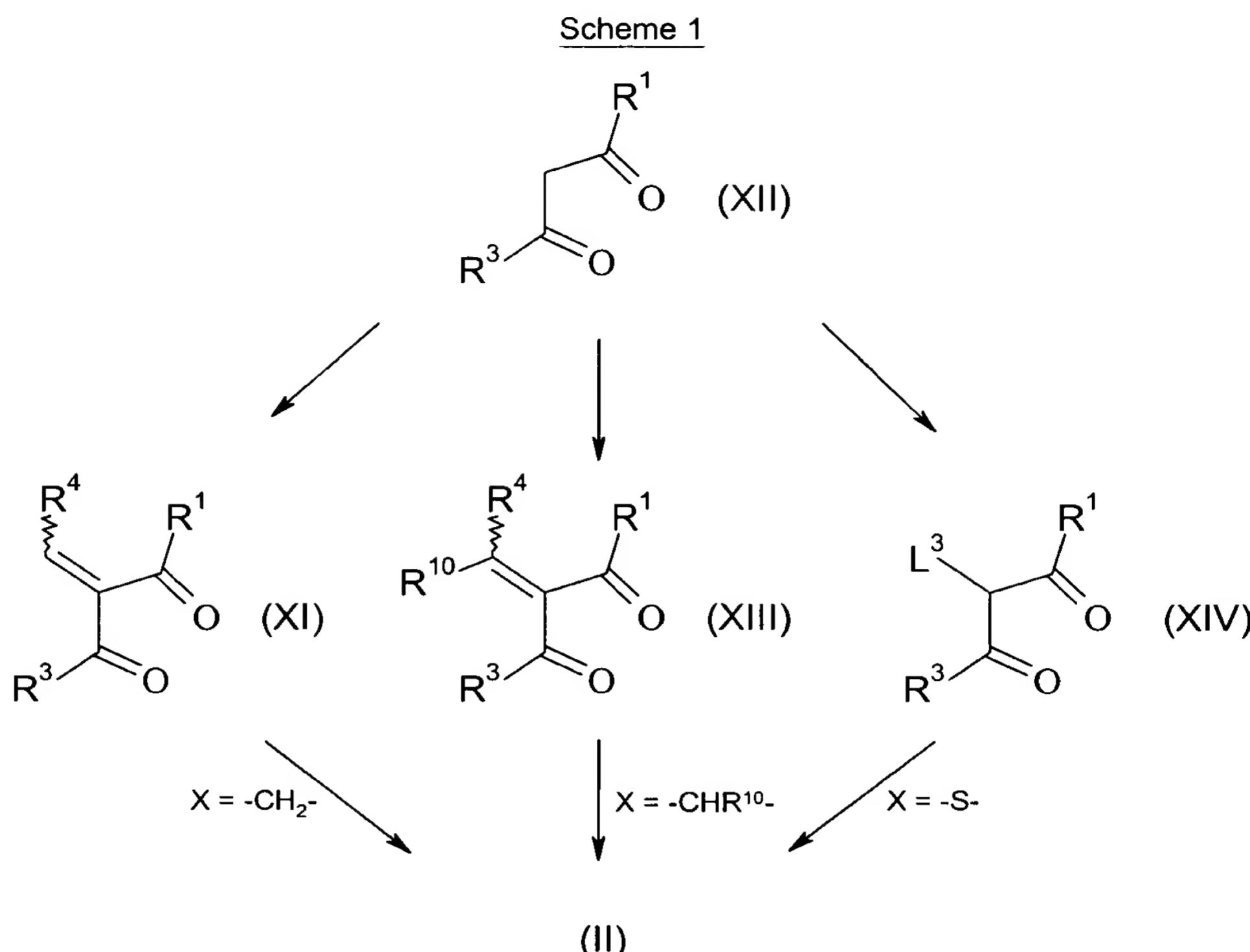
15 In a typical procedure a solution of a compound of the formula (VIII) in a suitable solvent, such as acetone, is treated with a compound of the formula (IX), optionally treated with a base, such as potassium carbonate and optionally treated with a catalyst such as sodium iodide or tetrabutylammonium iodide. The reaction is preferably performed at room temperature.

20 Compounds of the formula (VII) are either commercially available or may be prepared from a compound of the formula



and a compound of the formula (IX) in the same way that a compound of the formula (VI) may be prepared from a compound of the formula (VIII).

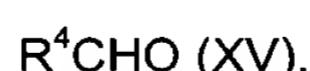
25 Compounds of the formula (II) may be prepared using the route shown in Scheme 1
in which L³ is a suitable leaving group, preferably chloro.



In Scheme 1, compounds of the formula (II) in which X is $-\text{CH}_2-$ may be prepared by

5 the reduction of a compound of the formula (XI) with a suitable reducing agent such as (a)
hydrogen in the presence of a palladium catalyst, (b) diphenylsilane in the presence of a
palladium catalyst and a zinc salt or (c) triethylsilane in the presence of an acid such as
trifluoroacetic acid. In a typical procedure, a solution of the compound of the formula (XI) in a
suitable solvent, such as ethanol or a mixture of ethanol and ethyl acetate, under a hydrogen
10 atmosphere, is treated with 5% w/w palladium on barium sulphate. In another typical
procedure, a solution of the compound of the formula (XI) in a suitable solvent, such as
dichloromethane, is treated with diphenylsilane, tetrakis(triphenylphosphine)palladium (0) and
zinc chloride. In a further typical example, a solution of the compound of the formula (XI) in a
suitable solvent, such as dichloromethane, is treated with triethylsilane and trifluoroacetic
15 acid.

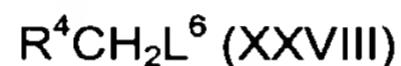
Compounds of the formula (XI) may be prepared by the condensation of a compound of the formula (XII) with a compound of the formula



or a functional equivalent thereof, such as an acetal, optionally in the presence of a
20 suitable catalyst, such as a mixture of acetic acid and piperidine. In a typical procedure, a
solution of the compound of the formula (XII) in a suitable solvent such as toluene is treated

with a compound of the formula (XV), acetic acid and piperidine and heated at a temperature of from room temperature to the reflux temperature of the solvent. Preferably, the reaction mixture is heated under reflux using a Dean-Stark apparatus. Compounds of the formula (XI), prepared in this way, in which R¹ and R³ are different, are usually formed as a mixture of 5 stereoisomers. Such a mixture may be used directly in subsequent transformations or separated into its individual stereoisomers which may then be used separately.

Alternatively, compounds of the formula (II) in which X is -CH₂- may be prepared by the reaction of a compound of the formula (XII) with a compound of the formula



10 in which L⁶ is a suitable leaving group, preferably is chloro, bromo, iodo or para-toluenesulphonate, in the presence of a suitable base. In a typical procedure, a solution of the compound of the formula (XII) in a suitable solvent, such as 2-butanone, tetrahydrofuran, acetonitrile or diethylether, is treated with a base, such as sodium ethoxide, sodium hydride or sodium carbonate, and the compound of the formula (XXVIII), optionally with heating. A 15 preferred combination is 2-butanone as the solvent and sodium hydride as the base.

Compounds of the formula (XII) and compounds of the formula (XXVIII) are either commercially available or are easily prepared by methods well known to the skilled person.

Compounds of the formula (II) in which X is -CHR¹⁰- (other than where R¹⁰ is C₁-C₆ alkoxy - see below for the preparation of these compounds) may be prepared by the reduction 20 of a compound of the formula (XIII) with a suitable reducing agent such as (a) hydrogen in the presence of a palladium catalyst, (b) diphenylsilane in the presence of a palladium catalyst and a zinc salt or (c) triethylsilane in the presence of an acid such as trifluoroacetic acid. In a typical procedure, a solution of the compound of the formula (XIII) in a suitable solvent, such as ethanol or a mixture of ethanol and ethyl acetate, under a hydrogen atmosphere, is treated 25 with 5% w/w palladium on barium sulphate. In another typical procedure, a solution of the compound of the formula (XIII) in a suitable solvent, such as dichloromethane, is treated with diphenylsilane, tetrakis(triphenylphosphine)palladium (0) and zinc chloride. In a further typical example, a solution of the compound of the formula (XIII) in a suitable solvent, such as dichloromethane, is treated with triethylsilane and trifluoroacetic acid.

30 Compounds of the formula (XIII) may be prepared by the condensation of a compound of the formula (XII) with a compound of the formula



or a functional equivalent thereof, such as a ketal, optionally in the presence of a suitable catalyst, such as a mixture of acetic acid and piperidine. In a typical procedure, a 35 solution of the compound of the formula (XII) in a suitable solvent such as toluene is treated with a compound of the formula (XVI), acetic acid and piperidine and heated at a temperature of from room temperature to the reflux temperature of the solvent. Preferably, the reaction

mixture is heated under reflux using a Dean-Stark apparatus. Compounds of the formula (XIII), prepared in this way, in which R¹ and R³ are different, are usually formed as a mixture of stereoisomers. Such a mixture may be used directly in subsequent transformations or separated into its individual stereoisomers which may then be used separately.

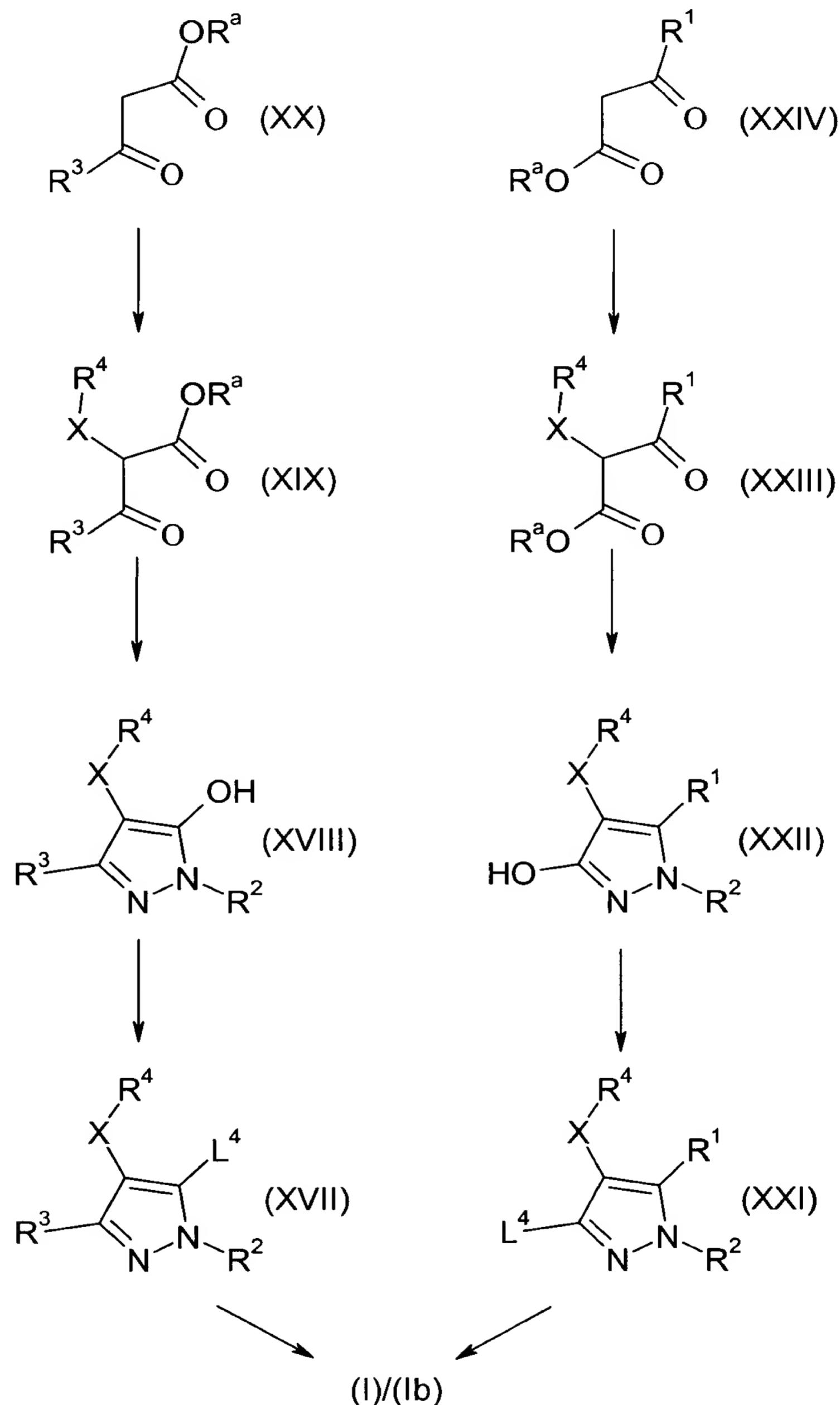
5 Compounds of the formula (II) in which X is -S- may be prepared by the reaction of a compound of the formula (XIV) with a compound of the formula (IX). In a typical procedure a solution of a compound of the formula (XIV) in a suitable solvent, such as acetone, is treated with a compound of the formula (IX), optionally treated with a base, such as potassium carbonate and optionally treated with a catalyst such as sodium iodide or tetrabutylammonium 10 iodide. The reaction is preferably performed at room temperature.

Compounds of the formula (XIV) may be prepared by the reaction of a compound of the formula (XII) with a suitable activating agent, e.g. in the case where L³ is chloro, with a chlorinating agent such as sulphuryl chloride. In a typical procedure, where L³ is chloro, the compound of the formula (XII) is treated with sulphuryl chloride, optionally in the presence of 15 a suitable solvent such as dichloromethane.

Compounds of the formula (Ib) and compounds of the formula (I) in which R¹ or R³ is -OR⁷ may be prepared using the route shown in Scheme 2 in which R^a is C₁-C₆ alkyl and L⁴ is a suitable leaving group, preferably trifluoromethanesulphonate.

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Scheme 2



In Scheme 2, compounds of the formula (Ib) and compounds of the formula (I) in which R¹ is -OR⁷ may be prepared by the reaction of a compound of the formula (XVII) with an alcohol of the formula

R^7OH (XXV)

in the presence of a suitable catalyst, preferably a palladium catalyst, and carbon monoxide. In a typical procedure a mixture of the compound of the formula (XVII), a suitable palladium catalyst such as 1,1'-bis(diphenylphosphino)ferrocenepalladium(II)chloride, the alcohol of the formula (XXV) and, optionally, a suitable solvent such as N,N-dimethylformamide is heated, preferably to about 50°C, under an atmosphere of carbon monoxide, preferably at a pressure of 345 kPa.

Compounds of the formula (XVII) may be prepared by the derivatisation of a compound of the formula (XVIII). In the case where L⁴ is trifluoromethanesulphonate a suitable derivatising agent is phenyltriflame. In a typical procedure, where L⁴ is trifluoromethanesulphonate, a solution of the compound of the formula (XVIII) and a suitable base, preferably a trialkylamine base such as triethylamine, in a suitable solvent such as dichloromethane is treated with phenyltriflame.

Compounds of the formula (XVIII) may be prepared by the reaction of a compound of the formula (XIX) with a compound of the formula (III), or a salt or hydrate thereof, optionally in the presence of an acid or a base, the base preferably being a tertiary amine base such as triethylamine and the acid preferably being acetic acid. In a typical procedure, a solution of the compound of the formula (XIX) in a suitable solvent, such as ethanol, is treated with the compound of the formula (III), or the salt or hydrate thereof, and, if used, the appropriate acid or base, at a temperature of from room temperature to the reflux temperature of the solvent. In a preferred procedure, the reaction mixture is heated under reflux.

Compounds of the formula (XIX) may be prepared by the derivatisation of a compound of the formula (XX) in the same way that compounds of the formula (II) may be prepared by the derivatisation of a compound of the formula (XII) as described above.

Compounds of the formula (XX) are either commercially available or are readily prepared by methods well known to the skilled person.

In Scheme 2, compounds of the formula (Ib) and compounds of the formula (I) in which R³ is -OR⁷ may be prepared from a compound of the formula (XXIV) in the same way that a compound of the formula (I) or a compound of the formula (Ib) in which R¹ is -OR⁷ is prepared from a compound of the formula (XX), as described above, *mutatis mutandis*.

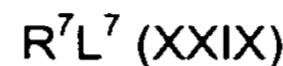
The skilled man will appreciate that compounds of the formula (XVIII) and compounds of the formula (XXII) may exist in one of several tautomeric forms.

Alternatively, compounds of the formula (Ib) and compounds of the formula (I) in which R¹ or R³ is -OR⁷ may be prepared from compounds of the formula (XVIII) or (XXII), respectively, by reaction with a compound of the formula (XXV) under dehydrating conditions, e.g. using the Mitsunobu reaction. In a typical procedure, a solution of the compound of the formula (XVIII) or (XXII) in a suitable solvent, such as tetrahydrofuran is treated with a

dialkylazodicarboxylate, preferably diethylazodicarboxylate, a triarylphosphine, preferably triphenylphosphine and a compound of the formula (XXV).

Alternatively, compounds of the formula (Ib) and compounds of the formula (I) in which R¹ or R³ is -OR⁷ may be prepared from compounds of the formula (XVIII) or (XXII),

5 respectively, by reaction with a compound of the formula



in which L⁷ is a suitable leaving group, preferably halo, optionally in the presence of a suitable base. In a typical procedure, a solution of the compound of the formula (XVIII) or the compound of the formula (XXII) in a suitable solvent, such as tetrahydrofuran,

10 dimethylformamide or ethanol, is treated with a base, such as sodium ethoxide or sodium carbonate, and the compound of the formula (XXIX), optionally with heating.

Compounds of the formula (Ib) and compounds of the formula (I) in which R¹ or R³ is halo may be prepared by the reaction, respectively, of a compound of the formula (XVIII) or a

compound of the formula (XXII) with a suitable halogenating agent. In a typical procedure, the

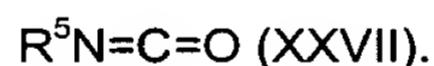
15 compound of the formula (XVIII) or (XXII) is treated with POCl₃, optionally in the presence of a suitable solvent such as dimethylformamide, to give a compound of the formula (Ib) or a compound of the formula (I) in which R¹ or R³, respectively, is chloro.

Compounds of the formula (Ib) and compounds of the formula (I) in which R¹ or R³ is -OCONR⁵R⁵ may be prepared by the reaction, respectively, of a compound of the formula

20 (XVIII) or a compound of the formula (XXII) with a compound of the formula

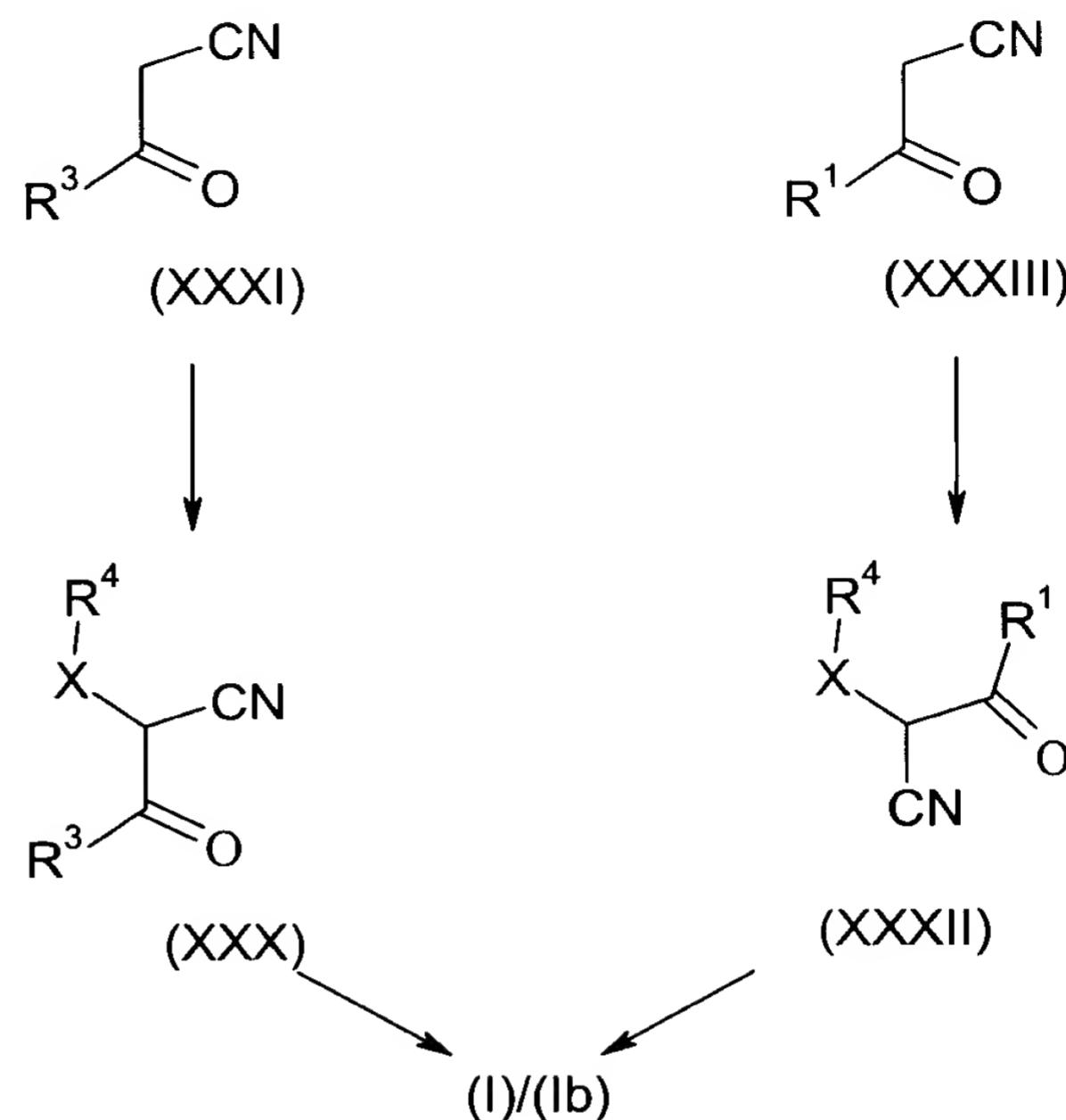


in which L⁵ is a suitable leaving group, preferably chloro, or, in the case where one of the R⁵ groups is H, with a compound of the formula



25 Compounds of the formula (Ib) and compounds of the formula (I) in which R¹ or R³ is -NH₂ may be prepared by the route shown in Scheme 3.

Scheme 3



5 In Scheme 3, compounds of the formula (Ib) and compounds of the formula (I) in
 which R^1 is $-\text{NH}_2$ may be prepared by the reaction of a compound of the formula (XXX) with a
 compound of the formula (III), or a salt or hydrate thereof, optionally in the presence of an
 acid or a base, the base preferably being a tertiary amine base such as triethylamine and the
 acid preferably being acetic acid. In a typical procedure, a solution of the compound of the
 10 formula (XXX) in a suitable solvent, such as ethanol, is treated with the compound of the
 formula (III), or the salt or hydrate thereof, and, if used, the appropriate acid or base, at a
 temperature of from room temperature to the reflux temperature of the solvent. In a preferred
 procedure, the reaction mixture is heated under reflux.

Compounds of the formula (XXX) may be prepared from a compound of the formula (XXXI)
 15 (XXXI) in the same way that compounds of the formula (II) may be prepared from a
 compound of the formula (XII) as described above.

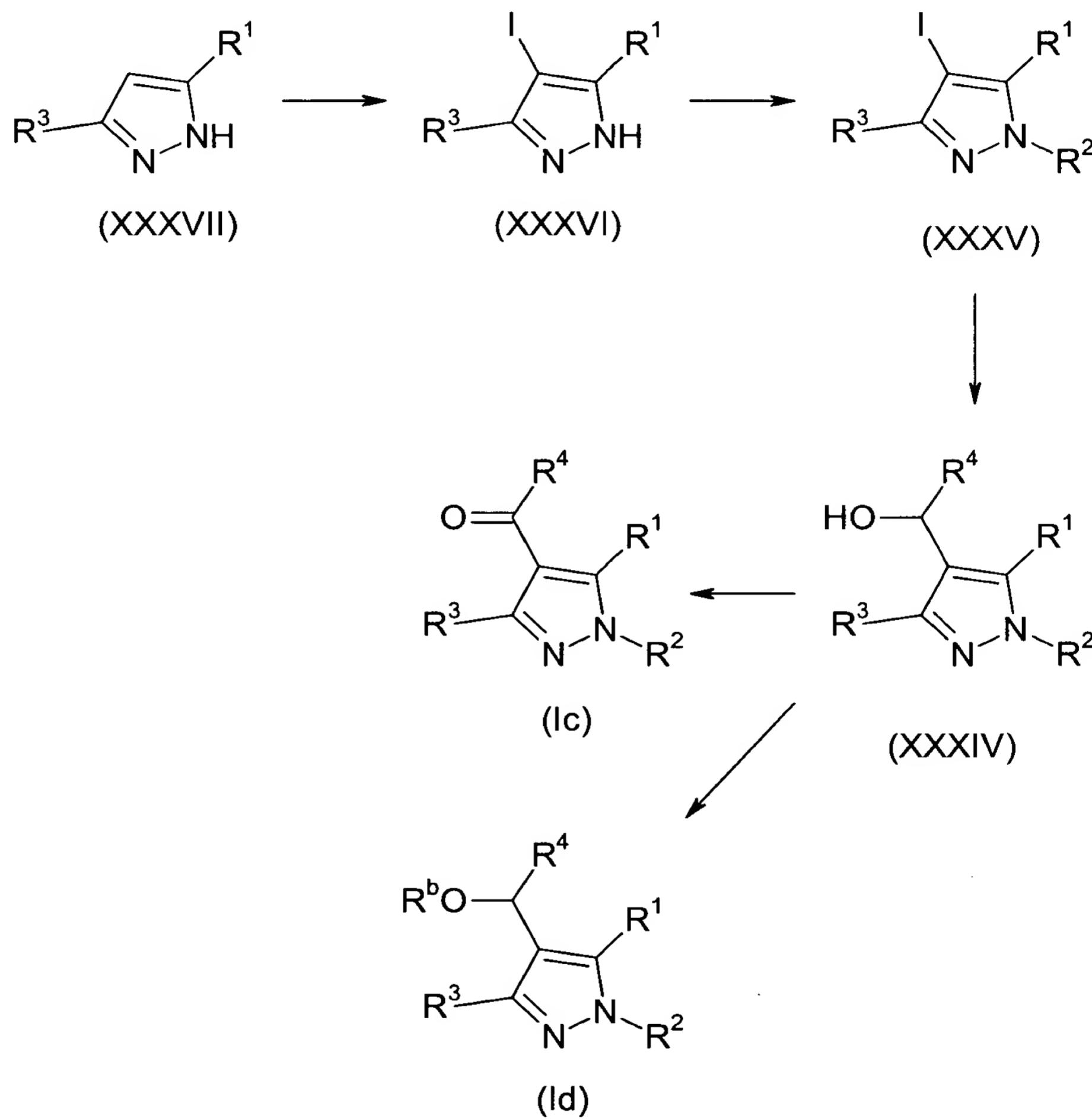
Compounds of the formula (XXXI) are either commercially available or readily
 prepared by methods well known to the skilled person.

In Scheme 3, compounds of the formula (Ib) and compounds of the formula (I) in
 20 which R^3 is $-\text{NH}_2$ may be prepared from a compound of the formula (XXXIII) in the same way
 that compounds of the formula (Ib) and compounds of the formula (I) in which R^1 is NH_2 may
 be prepared from compounds of the formula (XXXI), *mutatis mutandis*.

Compounds of the formula (Ib) and compounds of the formula (I) in which X is -CO- or -CHR¹⁰- and R¹⁰ is C₁-C₆ alkoxy may be prepared by the route shown in Scheme 4 in which R^b is C₁-C₆ alkyl.

5

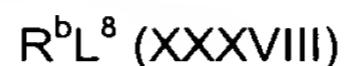
Scheme 4



In Scheme 4, compounds of the formula (Ib) and compounds of the formula (I) in which X is -CO- (i.e. compounds of the formula (Ic)) may be prepared by the oxidation of a compound of the formula (XXXIV). In a typical procedure, a solution of a compound of the formula (XXXIV) in a suitable solvent, such as dichloromethane, is treated with N-methylmorpholine-N-oxide and tetra-n-propylammonium perruthenate^(VII).

Compounds of the formula (Ib) and compounds of the formula (I) in which X is -CHR¹⁰- and R¹⁰ is C₁-C₆ alkoxy (i.e. compounds of the formula (Id)) may be prepared by the alkylation of a compound of the formula (XXXIV). In a typical procedure, a solution of a

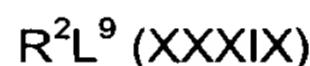
compound of the formula (XXXIV) in a suitable solvent, such as N,N-dimethylformamide, is treated with a base, such as sodium hydride, and a compound of the formula



wherein R^b is C₁-C₆ alkyl and L^8 is a suitable leaving group, preferably chloro, bromo or iodo.

Compounds of the formula (XXXIV) may be prepared by the reaction of a compound of the formula (XXXV) with a suitable metal or organometallic reagent to form an organometallic intermediate which is reacted with a compound of the formula (XV). A preferred metal is magnesium. In a typical procedure, a solution of the compound of the formula (XXXV) in a suitable solvent, such as tetrahydrofuran, is treated with an alkylmagnesium chloride, e.g. iso-propylmagnesium chloride, preferably with cooling in an ice bath, and a compound of the formula (XV) is added.

Compounds of the formula (XXXV) may be prepared by the reaction of a compound of the formula (XXXVI) with a suitable base, preferably sodium hydride, and the addition of a compound of the formula



wherein L^9 is a suitable leaving group, preferably a chloro, bromo, iodo or tosylate group. In a typical procedure, a solution of the compound of the formula (XXXVI) in a suitable solvent, such as N,N-dimethylformamide, is treated firstly with a suitable base, such as sodium hydride, and then with a compound of the formula (XXXIX). The reaction is then preferably heated, most preferably to 50°C. If R^2 contains a free -OH, -NH₂, or -NH- group then a protecting group is preferably employed to mask such functionality. Examples of suitable protecting groups will be apparent to the skilled person [see, for instance, 'Protecting groups in Organic Synthesis (Second Edition)' by Theodora W. Green and Peter G. M. Wuts, 1991, John Wiley and Sons]. The protecting group may be removed immediately or carried through subsequent steps, as described above, and removed as a final step (see below).

Compounds of the formula (XXXVI) may be prepared by the reaction of a compound of the formula (XXXVII) with a suitable iodinating agent. In a typical procedure, a solution of the compound of the formula (XXXVII) in a suitable solvent, such as dichloromethane, is treated with the iodinating agent which is preferably N-iodosuccinimide.

Compounds of the formula (XXXVII) are either commercially available or are readily prepared by methods well known to the skilled man. Such compounds may, for instance, be prepared by analogy with the methods presented above, for example by the reaction of a diketone (XII) with a compound of the formula (III), or a salt or solvate thereof.

It will be appreciated by those skilled in the art that, in many cases, compounds of the formula (Ib) and compounds of the formula (I) may be converted, respectively, into other

compounds of the formula (Ib) or compounds of the formula (I) by functional group transformations. For instance:

(a) Compounds of the formula (Ib)/(I) in which R² is H may be converted into compounds of the formula (Ib)/(I) in which R² is optionally substituted C₁-C₆ alkyl by reaction 5 with an appropriate alkylating agent. In a typical procedure, a solution of a compound of the formula (Ib)/(I) in which R² is H in a suitable solvent such as ethanol or N,N-dimethylformamide is treated with an alkyl bromide and a base such as sodium ethoxide or sodium hydride and heated at a temperature of from room temperature to the reflux 10 temperature of the solvent. A preferred combination is N,N-dimethylformamide as the solvent, sodium hydride as the base and room temperature as the temperature. Examples of specific alkylating agents include bromoacetonitrile, ethyl 4-chloroacetoacetate, ethyl bromoacetate, methyl bromoacetate and chloroethylamine hydrochloride. The use of further specific alkylating agents is illustrated by the Examples below.

(b) Compounds of the formula (Ib)/(I) in which R² contains an ester functionality 15 may be reduced with a suitable reducing agent, such as lithium aluminium hydride, to give corresponding compounds of the formula (Ib)/(I) in which R² contains a hydroxy group. In a typical procedure, a solution of the compound of the formula (Ib)/(I), in which R² contains an ester group, in a suitable solvent, such as diethyl ether, is treated with lithium aluminium hydride, preferably with cooling to a temperature of from -78 °C to 0 °C.

(c) Compounds of the formula (Ib)/(I) in which R¹ or R³ is -NH₂, may be 20 converted into compounds of the formula (Ib)/(I) in which R¹ or R³, respectively, is -NHR^c, where R^c is C₁-C₆ alkyl, C₃-C₈ cycloalkyl or benzyl by a reductive amination with an appropriate aldehyde or ketone. In a typical reductive amination, the reaction will proceed in a suitable solvent such as dichloromethane, in the presence of a suitable reducing agent such 25 as sodium triacetoxyborohydride and optionally in the presence of an acid such as acetic acid. A further reductive amination may be performed on a compound of the formula (Ib)/(I) in which R¹ or R³ is -NHR^c to give a compound of the formula (Ib)/(I) in which R¹ or R³, respectively, is -NR^cR^c, where R^c is as defined above and each R^c may be the same or different.

(d) Compounds of the formula (Ib)/(I) in which R¹ or R³ is -NHR⁵, may be 30 converted into compounds of the formula (Ib)/(I) in which, respectively, R¹ is -NR⁵COR⁵, -NR⁵CONR⁵R⁵, -NR⁵CO₂R⁷ or -NR⁵SO₂R⁷ or R³ is -NR⁵COR⁵, -NR⁵CONR⁵R⁵, -NR⁵CO₂R⁷ or -NR⁵SO₂R⁷ by reaction with an appropriate acylating or sulphonylating agent in a suitable inert solvent, such as dichloromethane, optionally in the presence of a base, preferably a tertiary amine base such as triethylamine.

(e) Compounds of the formula (Ib)/(I) in which R¹ or R³ is -CO₂R⁵, wherein R⁵ is other than H, may be converted into compounds of the formula (Ib)/(I) in which R¹ or R³,

respectively, is $-\text{CO}_2\text{H}$ by hydrolysis. Typically the reaction will be carried out in a suitable solvent, such as aqueous ethanol, or aqueous 1,4-dioxan and in the presence of a base such as sodium hydroxide. Such an acid may be converted to a primary amide by reaction with ammonia and a suitable coupling agent, such as a carbodiimide, e.g. 5 dicyclohexylcarbodiimide. Such a primary amide may then be converted into a nitrile by dehydration with a suitable dehydrating agent, such as phosphoryl chloride.

(f) Compounds of the formula (Ib)/(I) in which R^1 or R^3 is $-\text{CO}_2\text{H}$, may be converted into compounds of the formula (Ib)/(I) in which R^1 or R^3 , respectively, is $-\text{NH}_2$, by the Curtius rearrangement. In a typical procedure, the reaction is carried out in a suitable solvent, 10 such as dichloromethane, in the presence of a reagent such as diphenylphosphoryl azide.

(g) Compounds of the formula (Ib)/(I) in which X is $-\text{S}-$ may be converted into compounds of the formula (Ib)/(I) in which X is $-\text{SO}-$ by reaction with a suitable oxidising agent, such as meta-chloroperoxybenzoic acid. The reaction is carried out in the presence of a suitable solvent such as dichloromethane.

(h) Compounds of the formula (Ib)/(I) in which X is $-\text{S}-$ may be converted into compounds of the formula (Ib)/(I) in which X is $-\text{SO}_2-$ by reaction with a suitable oxidising agent such as Oxone (trade mark), meta-chloroperoxybenzoic acid or hydrogen peroxide. In a typical procedure, a solution of the compound of the formula (Ib)/(I) in which X is $-\text{S}-$ in a suitable solvent, such as dichloromethane, is treated with meta-chloroperoxybenzoic acid.

(i) Compounds of the formula (Ib)/(I) in which R^1 , R^2 or R^3 contain a heterocycle of the formula R^6 may be prepared by standard heterocycle-forming reactions well known to the skilled person (see, for example, Advanced Organic Chemistry, 3rd Edition, by Gerry March or Comprehensive Heterocyclic Chemistry, A.R. Katritzky, C.W. Rees, E.F.V. Scriven, Volumes 1-11), either from another compound of the formula (Ib)/(I) or otherwise. For 25 instance, compounds of the formula (Ib)/(I) in which R^2 is (2-amino-6-hydroxypyrimidin-4-yl)methyl may be prepared by the sequential reaction of a compound of the formula (Ib)/(I) in which R^2 is H with methyl 4-chloroacetoacetate and then guanidine hydrochloride.

(j) Compounds of the formula (Ib)/(I) in which either R^1 or R^3 is an N-linked heterocycle of the formula R^6 may be prepared from compounds of the formula (Ib)/(I) in 30 which R^1 or R^3 , respectively, is $-\text{NH}_2$, by standard heterocycle-forming reactions well known to the skilled man (see, for example, Advanced Organic Chemistry, 3rd Edition, by Gerry March or Comprehensive Heterocyclic Chemistry, A.R. Katritzky, C.W. Rees, E.F.V. Scriven, Volumes 1-11).

Compounds of the formula (Ib)/(I) containing an $-\text{OH}$, $-\text{NH}-$ or $-\text{NH}_2$ group may be prepared by the deprotection of the corresponding compound bearing an $-\text{OP}^1$, $-\text{NP}^1-$ or 35 $-\text{NHP}^1$ group, respectively, wherein the group P^1 is a suitable protecting group. Examples of suitable protecting groups will be apparent to the skilled person [see, for instance, 'Protecting

groups in Organic Synthesis (Second Edition)' by Theodora W. Green and Peter G. M. Wuts, 1991, John Wiley and Sons]. Such compounds bearing an -OP¹, -NP¹- or -NHP¹ group may be prepared using the routes described above, *mutatis mutandis*.

The compounds of the formula (I) and the compounds of the formula (Ib) can be
5 administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, the compounds of the formula (I) and the compounds of the formula (Ib)
can be administered orally, buccally or sublingually in the form of tablets, capsules,
10 particulates, gels, films, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications. The compounds of the formula (I) and the compounds of the formula (Ib) may also be administered as fast-dispersing or fast-dissolving dosage forms or in the form of a high energy dispersion or as coated particles. Suitable formulations of the
15 compounds of the formula (I) and the compounds of the formula (Ib) may be in coated or uncoated form, as desired.

Such solid pharmaceutical compositions, for example, tablets, may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycine and starch (preferably corn, potato or tapioca starch), disintegrants such
20 as sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

General Example

25 A formulation of the tablet could typically contain between about 0.01mg and 500mg of active compound whilst tablet fill weights may range from 50mg to 1000mg. An example of a formulation for a 10mg tablet is illustrated below:

	<u>Ingredient</u>	<u>%w/w</u>
	Compound of the formula (I)/(Ib) or salt	10.000*
30	Lactose	64.125
	Starch	21.375
	Croscarmellose sodium	3.000
	Magnesium Stearate	1.500

35 * Quantity adjusted in accordance with drug activity.

The tablets are manufactured by a standard process, for example, direct compression or a wet or dry granulation process. The tablet cores may be coated with appropriate overcoats.

Solid compositions of a similar type may also be employed as fillers in gelatin or HPMC capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compounds of the formula (I) and the compounds of the formula (Ib) may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

The compounds of the formula (I) and the compounds of the formula (Ib) can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion or needleless injection techniques. For such parenteral administration they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of the formula (I) and the compounds of the formula (Ib) will usually be from 0.01 to 30 mg/kg, preferably from 0.01 to 10 mg/kg (in single or divided doses).

Thus tablets or capsules of the compound of the formula (I) or the compound of the formula (Ib) may contain from 1 to 500 mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention. The skilled person will appreciate that, in the treatment of certain conditions the compounds of the formula (I) and the compounds of the formula (Ib) may be taken as a single dose as needed or desired.

The compounds of formula (I) and the compounds of the formula (Ib) can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomiser or nebuliser, with or without the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a

hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray, atomiser or nebuliser

5 may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the formula (I) or a compound of the formula (Ib) and a suitable powder base such as lactose or starch.

10 Alternatively, the compounds of the formula (I) and the compounds of the formula (Ib) can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder. The compounds of the formula (I) and the compounds of the formula (Ib) may also be dermally or transdermally administered, for example, by the use of a skin patch. They may also be

15 administered by the pulmonary or rectal routes.

They may also be administered by the ocular route. For ophthalmic use, the compounds can be formulated as micronised suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, they may

20 be formulated in an ointment such as petrolatum.

For application topically to the skin, the compounds of the formula (I) and the compounds of the formula (Ib) can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene

25 polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

30 The compounds of the formula (I) and the compounds of the formula (Ib) may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes.

35 As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-

cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

5 Oral administration is preferred.

Included within the scope of the present invention are embodiments comprising the co-administration of a compound of the present invention with one or more additional therapeutic agents, and compositions containing a compound of the present invention along with one or more additional therapeutic agents. Such a combination therapy is especially
10 useful for the treatment of infection by HIV and related retroviruses which may evolve rapidly into strains resistant to any monotherapy. Alternatively, additional therapeutic agents may be desirable to treat diseases and conditions which result from or accompany the disease being treated with the compound of the present invention. For example, in the treatment of an HIV or related retroviral infection, it may be desirable to additionally treat opportunistic infections,
15 neoplasms and other conditions which occur as a result of the immuno-compromised state of the patient being treated.

Preferred combinations of the present invention include simultaneous or sequential treatment with a compound of the formula (I) or a compound of the formula (Ib), as defined above, or a pharmaceutically acceptable salt thereof, and:

20 (a) one or more reverse transcriptase inhibitors such as zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, adefovir, combivir or trizivir;

 (b) one or more non-nucleoside reverse transcriptase inhibitors such as nevirapine, delavirdine or efavirenz;

25 (c) one or more HIV protease inhibitors such as indanivir, ritonavir, saquinavir or nelfinavir;

 (d) one or more CCR5 antagonists such as TAK-779 or SCH-351125;

 (e) one or more CXCR4 antagonists such as AMD-3100;

 (f) one or more integrase inhibitors;

 (g) one or more inhibitors of viral fusion such as T-20 or T-1249;

30 (h) one or more investigational drugs such as KNI-272, amprenavir, GW-33908, FTC, PMPA, S-1153, MKC-442, MSC-204, MSH-372, DMP450, PNU-140690, ABT-378, KNI-764, DPC-083, TMC-120 or TMC-125; or

 (i) one or more antifungal or antibacterial agents such as fluconazole.

The activity of the compounds of the invention as reverse transcriptase inhibitors and
35 as agents for treating HIV infections may be measured using the following assays.

A. Inhibition of HIV-1 reverse transcriptase enzyme

The reverse transcriptase activity of the compounds of the invention may be assayed as following. Using the purified recombinant HIV-1 reverse transcriptase (RT, EC, 2.7.7.49) obtained by expression in Escherichia Coli, a 96-well plate assay system was established for 5 assaying a large number of samples using either the Poly(rA)-oligo(dT) Reverse Transcriptase [3H]-SPA enzyme assay system (Amersham NK9020) or the [3H]-flashplate enzyme assay system (NEN - SMP 103) and following the manufacturer's recommendations. The compounds were dissolved in 100% DMSO and diluted with the appropriate buffer to a 5% final DMSO concentration. The inhibitory activity was expressed in percent inhibition 10 relative to the DMSO control. The concentration at which the compound inhibited the reverse transcriptase by 50% was expressed as the IC₅₀ of the compound.

B. Anti-Human Immunodeficiency Virus (HIV-1) cell culture assay

The anti-HIV activity of the compounds of the invention may be assayed by the following procedures.

15 1) SupT1 cells were cultured in an RPMI-1640 medium supplemented with 10% foetal calf serum and were split so that they were in growth phase on the day of use.

2) The compounds were dissolved in 100% DMSO and diluted with the above culture medium to predetermined concentrations and distributed in 20µl aliquots into a 96-well microtiter plate (0.1% DMSO final concentration).

20 3) To prepare infected cells, 100µl of RF viruses (TCID₅₀ of 10⁷/ml) were added to 10⁶ cells and incubated for 1 hour at 37°C. The cells were then washed twice in PBS and resuspended in the culture medium at a density of 2.2 x10⁵cells/ml. 180µl of these infected cells was transferred to wells of the 96 well plate containing the compounds.

25 4) The plate was incubated in a CO₂ incubator at 37°C for 4 days. The cell survival rates were measured following the manufacturer's recommendations (CellTiter 96® AQ_{ueous} Non-Radioactive Assay - Promega (cat no: G5430)). The concentration at which the compound inhibited the cytotoxic effect of the virus by 50% was expressed as the EC₅₀.

Thus the invention provides:

- (i) the use of a compound of the formula (I) or a compound of the formula (Ib) or a pharmaceutically acceptable salt or solvate of either in the manufacture of a reverse transcriptase inhibitor or modulator;
- 5 (ii) the use of a compound of the formula (I) or a compound of the formula (Ib), or a pharmaceutically acceptable salt or solvate of either in the manufacture of a medicament for the treatment of a human immunodeficiency viral (HIV), or genetically related retroviral, infection or a resulting acquired immunodeficiency syndrome (AIDS);
- 10 (iii) a compound of the formula (I) or a compound of the formula (Ib), or a pharmaceutically acceptable salt or solvate of either, for use as a reverse transcriptase inhibitor;
- (iv) a compound of the formula (I) or a compound of the formula (Ib) or a pharmaceutically acceptable salt or solvate of either, for use in the treatment of a human immunodeficiency viral (HIV), or genetically related retroviral, infection or a resulting acquired immunodeficiency syndrome (AIDS);
- 15 (v) a method of treatment or prevention of a disorder treatable by the inhibition of reverse transcriptase, comprising the administration of an effective amount of a compound of the formula (I) or a compound of the formula (Ib), or a pharmaceutically acceptable salt or solvate of either, to a patient in need of such treatment;
- 20 (vi) a method of treatment of a human immunodeficiency viral (HIV), or genetically related retroviral, infection or a resulting acquired immunodeficiency syndrome (AIDS) comprising the administration of an effective amount of a compound of the formula (I) or a compound of the formula (Ib), or a pharmaceutically acceptable salt or solvate of either, to a patient in need of such treatment;
- 25 (vii) a compound of the formula (Ib) or a pharmaceutically acceptable salt or solvate thereof;
 - (viii) a process for the preparation of a compound of the formula (Ib) or a pharmaceutically acceptable salt or solvate thereof;
- 30 (ix) a pharmaceutical composition including a compound of the formula (Ib) or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient, diluent or carrier;
- (x) a compound of the formula (Ib) or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a medicament;

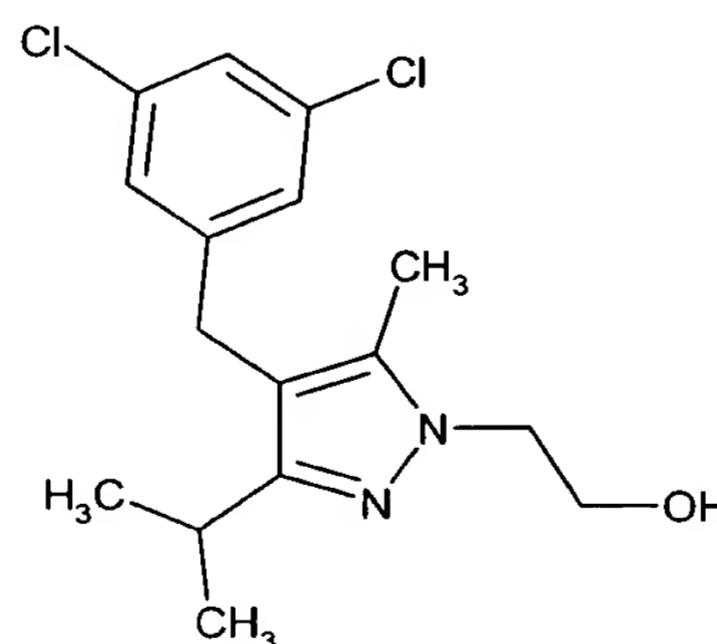
The following Examples illustrate the preparation of the compounds of the formula (I) and the compounds of the formula (II). The synthesis of certain intermediates used therein are described in the Preparations section that follows the Examples.

¹H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The following abbreviations have been used: HRMS, high resolution mass spectrometry; hplc, high performance liquid chromatography; nOe, nuclear Overhauser effect; m.p., melting point; h, hour; Et, ethyl; CDCl₃, deuteriochloroform; D₆-DMSO, deuteriodimethylsulphoxide; CD₃OD, deuteromethanol; THF, tetrahydrofuran. '0.880 Ammonia solution' means a concentrated aqueous solution of ammonia having a specific gravity of 0.88. Where thin layer chromatography (TLC) has been used it refers to silica gel TLC using silica gel 60 F₂₅₄ plates, R_f is the distance travelled by a compound divided by the distance travelled by the solvent front on a TLC plate. In certain of the Examples there is the possibility of regioisomerism in the product. The structures of certain Examples, for instance Examples 7 and 13 have been proven by nOe experiments. The regiochemistry of other Examples has been assigned by comparing characteristic shifts in their NMR spectra with the corresponding shifts in the NMR spectra of Examples 7 and 13.

20

EXAMPLE 1

2-[4-(3,5-Dichlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]ethanol



25 A solution of the ester of Example 7 (170mg, 0.46mmol) in dry ether (3.5ml) was added to a suspension of lithium aluminium hydride (17.5mg, 0.46mmol) in dry ether (2ml) cooled to -78°C under nitrogen. After stirring at -78°C for 1hour and at 0°C for 1hour the reaction was quenched with water (5ml) and then partitioned between ether (30ml) and aqueous hydrochloric acid solution (pH=3, 30ml) and the aqueous layer was further extracted
30 with ether (2x30ml). The combined organic layers were dried over magnesium sulphate and

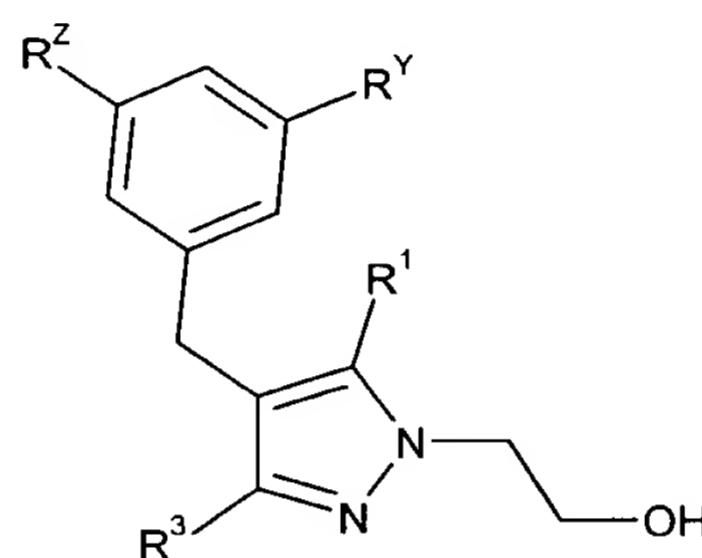
concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (2:1, by volume) to provide the title compound (116.3mg) as a white solid, m.p. 77-78°C.

5 $^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 1.18 (d, 6H), 2.08 (s, 3H), 2.80 (heptet, 1H), 3.75 (s, 2H), 4.00 (m, 2H), 4.06 (m, 2H), 4.19 (t, 1H), 6.97 (s, 2H), 7.18 (s, 1H).
HRMS (electrospray): m/z [MH $^+$] 327.1026 (calculated 327.1026).

EXAMPLES 2 to 6

The compounds of the following tabulated examples of the general formula:

10



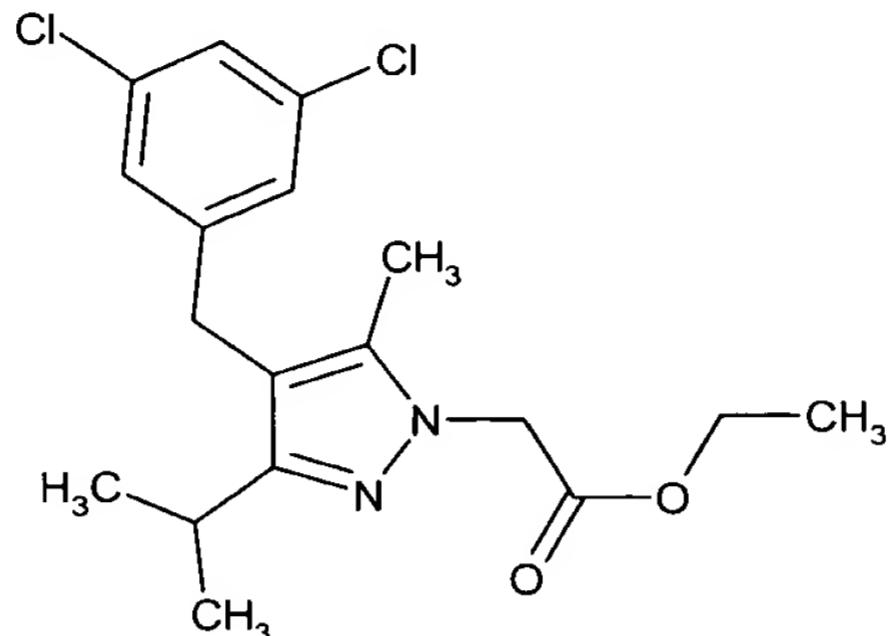
were prepared by a similar method to that of Example 1 using the appropriate esters.

Example No.	R ³	R'	R ^Z	R ^Y	LRMS m/z =	Analytical data, starting ester and variations in procedure.
2	CH ₃ CH ₂ -	CH ₃ CH ₂ -	Cl	Cl	[MH ⁺]	<p>¹H-NMR (300MHz, CDCl₃): δ = 1.06 (t, 3H), 1.18 (t, 3H), 2.50 (m, 4H), 3.72 (s, 2H), 4.05 (m, 2H), 4.12 (m, 2H), 4.19 (br. t, 1H), 6.99 (s, 2H), 7.19 (s, 1H).</p> <p>Contains ca. 10% monodechlorinated impurity as judged by LCMS (50x2mm Magellen 3 micron C18 column, solvent gradient 0.1%, by volume aqueous formic acid:0.1%, by volume formic acid in acetonitrile (95:5, by volume) to 0.1%, by volume aqueous formic acid:0.1%, by volume formic acid in acetonitrile (5:95, by volume), electrospray MS).</p> <p>Ester of Example 9.</p> <p>Chromatography with a solvent gradient of toluene:ethyl acetate (1:1, by volume) then toluene:ethyl acetate (1:2, by volume).</p>
3	CH ₃ CH(CH ₃)-	CH ₃ -	Cl	H	[MH ⁺]	<p>¹H-NMR (400MHz, CDCl₃): δ = 1.15 (d, 6H), 2.06 (s, 3H), 2.82 (m, 1H), 3.73 (s, 2H), 3.99 (m, 2H), 4.06 (m, 2H), 4.29 (br. s, 1H), 6.96 (m, 1H), 7.05 (s, 1H), 7.15 (m, 2H).</p> <p>Microanalysis: Found: C, 65.58; H, 7.30; N, 9.33. C₁₆H₂₁CIN₂O requires C, 65.63; H, 7.23; N, 9.57%.</p> <p>Ester of Example 15.</p> <p>Chromatography with a solvent gradient of pentane:ethyl acetate (2:1, by volume) then pentane:ethyl acetate (1:1, by volume).</p>

4	$\text{CH}_3\text{CH}(\text{CH}_3)\text{-}$	$\text{CH}_3\text{-}$	F	F	(electrospray): 295 [MH ⁺]	¹ H-NMR (400MHz, CDCl ₃): δ = 1.10 (d, 6H), 2.10 (s, 3H), 2.80 (heptet, 1H), 3.74 (s, 2H), 4.00 (m, 2H), 4.06 (m, 2H), 4.20 (t, 1H), 6.60 (m, 3H).
5	$\text{CH}_3\text{CH}(\text{CH}_3)\text{-}$	$\text{CH}_3\text{-}$	F	H	(thermospray): 277 [MH ⁺]	Ester of Example 16. Chromatography with a solvent gradient of pentane:ethyl acetate (2:1, by volume) then pentane:ethyl acetate (1:1, by volume). (heptet, 1H), 3.76 (s, 2H), 3.98 (m, 2H), 4.05 (m, 2H), 4.23 (t, 1H), 6.75 (d, 1H), 6.86 (m, 2H), 7.20 (m, 1H). Microanalysis: Found: C, 69.45; H, 7.71; N, 9.96. C ₁₆ H ₂₁ FN ₂ O requires C, 69.54; H, 7.66; N, 10.14%.
6	$\text{CH}_3\text{-}$	$\text{CH}_3\text{CH}(\text{CH}_3)\text{-}$	Cl	Cl	(thermospray): 327 [MH ⁺]	Ester of Example 10. Chromatography with pentane:ethyl acetate (1:1, by volume). (heptet, 1H), 3.79 (s, 2H), 4.00 (m, 2H), 4.13 (m, 2H), 6.95 (s, 2H), 7.18 (s, 1H). HRMS (electrospray): m/z [MH ⁺] 327.1031 (calculated 327.1026). Ester of Example 8, using Method B Chromatography with a solvent gradient of pentane:ethyl acetate (1:1, by volume) then ethyl acetate.

EXAMPLES 7 and 8

Ethyl [4-(3,5-dichlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]acetate (Example 7)



5 Method A:

A solution of 21% weight/volume sodium ethoxide in ethanol (227 μ L, 0.7mmol) was added dropwise to a stirred solution of the pyrazole of Example 17 (172.7mg, 0.61mmol) in dry ethanol (1ml) at room temperature in a Reacti-vial (Trade Mark) (a sealable reaction vessel; available from Pierce & Warriner (UK) Ltd). Ethyl bromoacetate (136 μ L, 1.22mmol) was added and the Reacti-vial (Trade Mark) was sealed and heated at 80°C for 2 hours and then stirred at room temperature for 16 hours. Further sodium ethoxide in ethanol (227 μ L, 0.7mmol) and ethyl bromoacetate (136 μ L, 1.22mmol) were added and the sealed mixture was heated for a further 7 hours. After cooling to room temperature further sodium ethoxide in ethanol (227 μ L, 0.7mmol) and ethyl bromoacetate (136 μ L, 1.22mmol) were added and the sealed mixture was heated for a further 10 hours. After cooling to room temperature the mixture was concentrated under reduced pressure and the residue was partitioned between water (30ml) and dichloromethane (30ml) and the aqueous layer was further extracted with dichloromethane (2x30ml). The combined organic layers were dried over magnesium sulphate and concentrated under reduced pressure and the crude product (321mg) was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (7:1, by volume) to provide Example 7 (175.3mg) as a white solid, m.p. 90-92°C.

¹H-NMR (400MHz, CDCl₃): δ = 1.18 (d, 6H), 1.27 (t, 3H), 2.06 (s, 3H), 2.81 (heptet, 1H), 3.74 (s, 2H), 4.22 (q, 2H), 4.83 (s, 2H), 6.96 (s, 2H), 7.17 (s, 1H). This structure was confirmed by nOe experiments.

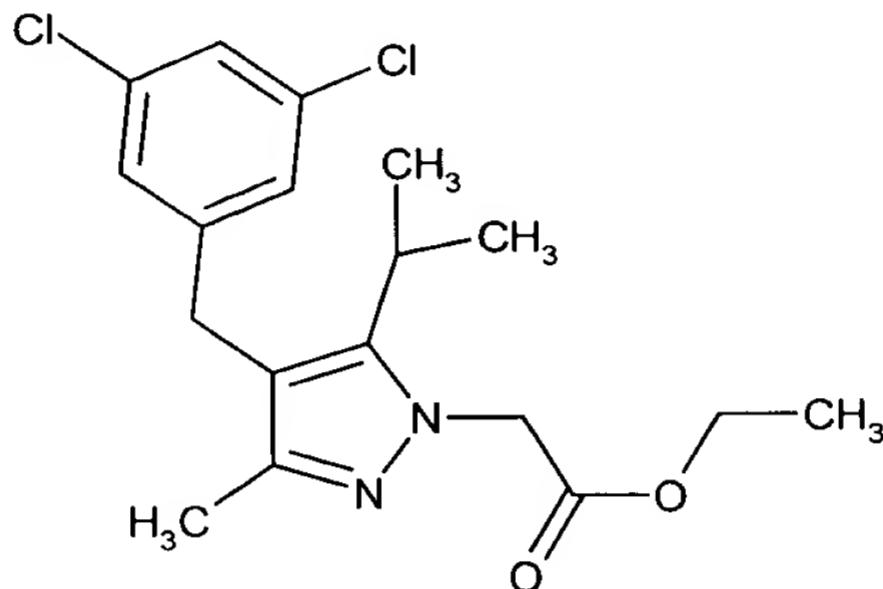
HRMS (electrospray): m/z [MH⁺] 369.1135 (calculated 369.1131).

Method B:

A solution of the β -diketone of Preparation 1 (245mg, 0.85mmol), ethyl hydrazinoacetate hydrochloride (132mg, 0.85mmol) and triethylamine (131 μ L, 0.94mmol) in

ethanol (1ml) was stirred and heated in a sealed Reacti-vial (Trade Mark) at 80°C for 24 hours. After cooling the mixture was concentrated under reduced pressure and the residue purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate (10:1, by volume) then pentane:ethyl acetate (5:1, by volume) to provide Example 7
5 (28.6mg) as a white solid, m.p. 94-95°C.

Further elution of the column afforded ethyl [4-(3,5-dichlorobenzyl)-5-isopropyl-3-methyl-1*H*-pyrazol-1-yl]acetate (Example 8) (228.8mg) as a yellow oil.

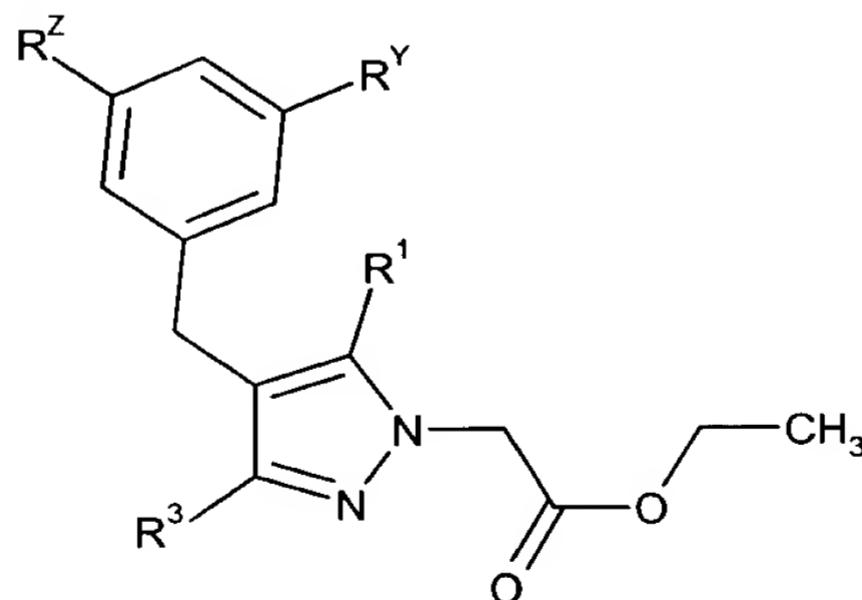


¹H-NMR (400MHz, CDCl₃): δ = 1.19 (d, 6H), 1.28 (t, 3H), 2.06 (s, 3H), 2.92 (heptet, 10 1H), 3.82 (s, 2H), 4.23 (q, 2H), 4.86 (s, 2H), 6.96 (s, 2H), 7.17 (s, 1H). This structure was confirmed by nOe experiments.

HRMS (electrospray): m/z [MH⁺] 369.1134 (calculated 369.1131).

EXAMPLES 9 to 10

15 The compounds of the following tabulated Examples of the general formula:

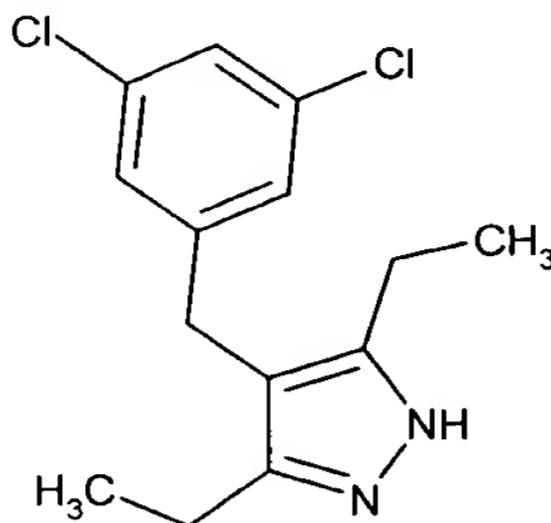


were prepared by a similar method to that of Example 7, Method A using the appropriate pyrazole.

Example No.	R^3	R^1	R^2	R^Y	LRMS m/z =	Analytical data, starting pyrazole and variations in procedure.
9	CH_3CH_2-	CH_3CH_2-	Cl	Cl	(thermospray): 369 [MH^+]	<p>1H-NMR (300MHz, $CDCl_3$): δ = 1.14 (t, 3H), 1.16 (t, 3H), 1.28 (t, 3H), 2.48 (m, 4H), 3.75 (s, 2H), 4.24 (q, 2H), 4.84 (s, 2H), 6.99 (s, 2H), 7.19 (s, 1H).</p> <p>Pyrazole of Example 11.</p> <p>Microanalysis: Found: C, 58.41; H, 5.95; N, 7.39. $C_{18}H_{22}Cl_2N_2O_2$ requires C, 58.54; H, 6.00; N, 7.59%.</p> <p>Contains ca. 10% monodechlorinated impurity as judged by LCMS. Chromatography with a solvent gradient of dichloromethane then dichloromethane:methanol (99:1, by volume).</p>
10	$CH_3CH(CH_3)-$	CH_3-	F	H	(thermospray): 319 [MH^+]	<p>1H-NMR (400MHz, $CDCl_3$): δ = 1.13 (d, 6H), 1.23 (t, 3H), 2.03 (s, 3H), 2.80 (heptet, 1H), 3.75 (s, 2H), 4.20 (q, 2H), 4.80 (s, 2H), 6.71 (d, 1H), 6.85 (m, 2H), 7.16 (m, 1H).</p> <p>HRMS (electrospray): m/z [MH^+] 319.1814 (calculated 319.1817).</p> <p>Pyrazole of Example 19.</p> <p>Chromatography with pentane:ethyl acetate (5:1, by volume).</p>

EXAMPLE 11

4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazole



Hydrazine hydrate (187 μ L, 3.85mmol) was added to a stirred solution of the β -diketone of Preparation 5 (1.00g, 3.5mmol) in ethanol (2.5ml) in a Reacti-vial (Trade Mark) at room temperature. The Reacti-vial (Trade Mark) was sealed and the mixture heated at 100°C for 3 hours. After cooling to room temperature the mixture was concentrated under reduced pressure to leave an oily white solid (1g) which was purified by flash chromatography on silica gel eluting with dichlormethane:methanol (98:2, by volume) to give the crude product which was recrystallised from diisopropylether (10ml) to give the title compound (150mg) as a white solid. LCMS analysis revealed a small amount (ca.10%) of monodechlorinated impurity carried through of Preparation 5. This impurity could be removed by hplc (150x21.2mm Phenomenex Luna C₁₈ 5 micron column, solvent gradient 0.1%, by volume aqueous diethylamine:methanol (90:10, by volume) to 0.1%, by volume aqueous diethylamine:methanol (10:90, by volume)) to afford pure title compound.

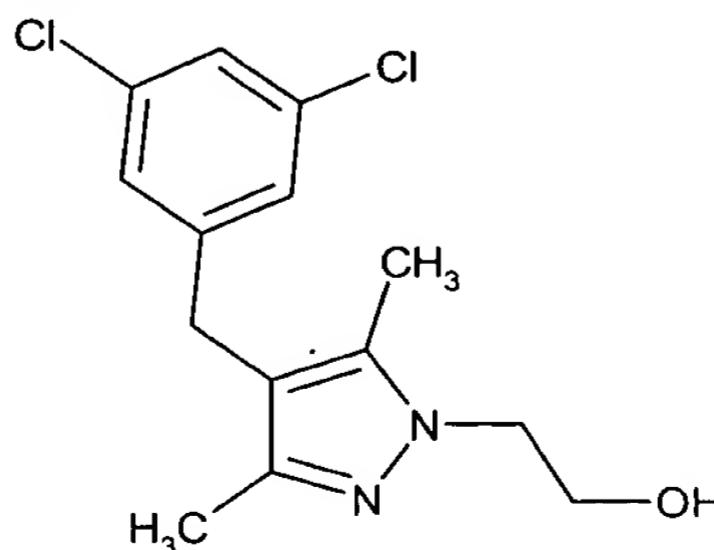
¹H-NMR (300MHz, CDCl₃): δ = 1.20 (t, 6H), 2.55 (q, 4H), 3.73 (s, 2H), 6.99 (s, 2H), 7.19 (s, 1H).

LRMS (thermospray): m/z [MH⁺] 283.

Microanalysis: Found: C, 59.53; H, 5.71; N, 9.82. C₁₄H₁₆Cl₂N₂ requires C, 59.38; H, 5.69; N, 9.89%.

EXAMPLE 12

2-[4-(3,5-Dichlorobenzyl)-3,5-dimethyl-1*H*-pyrazol-1-yl]ethanol



To a stirred suspension of the diketone of Preparation 4 (302mg, 1.17mmol) in ethanol (1ml) was added 2-hydroxyethyl hydrazine (81 μ L, 1.29mmol) and the resulting mixture was heated at 100°C in a sealed Reacti-vial (Trade Mark) for 6 hours. After cooling, the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate (1:2, by volume) then pentane:ethyl acetate (1:5, by volume) to afford the title compound (351mg) as a white powder.

10 $^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 2.08 (s, 3H), 2.11 (s, 3H), 3.62 (br. m, 1H), 3.66 (s, 2H), 4.00 (m, 2H), 4.07 (m, 2H), 6.95 (s, 2H), 7.16 (s, 1H).

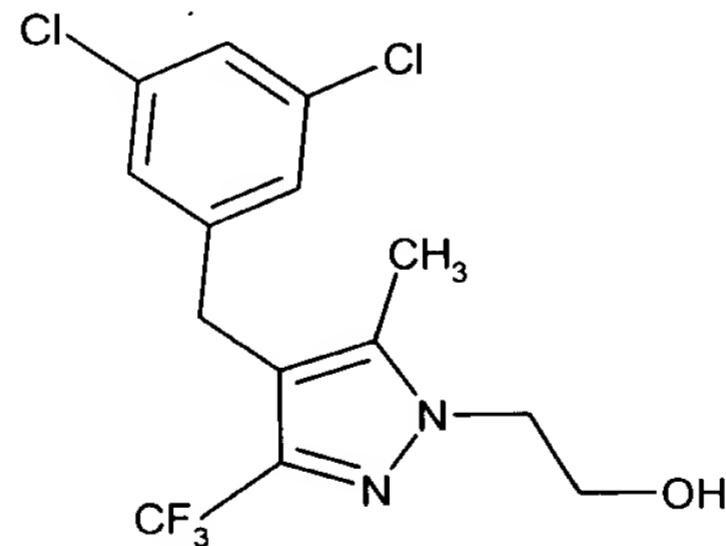
10 LRMS (thermospray): m/z [MH $^+$] 299.

Microanalysis: Found: C, 56.15; H, 5.38; N, 9.27. $\text{C}_{14}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}$ requires C, 56.20; H, 5.39; N, 9.36%.

15 LCMS analysis revealed a small amount (<10%) of dechlorinated impurities presumably arising from the reduction step in Preparation 4 but not detected at that stage. A portion of the product (190mg) was recrystallised from ethanol:water (2:1, by volume) (3ml) to afford a white solid (150mg). LCMS analysis then revealed only a trace amount (<5%) of mono-chlorinated product. This over reduction could probably be avoided by using the alternative reduction procedure of Preparation 6.

EXAMPLE 13

20 2-[4-(3,5-Dichlorobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanol



A solution of the diketone of Preparation 6 (76mg, 0.243mmol) in ethanol (2ml) was added to 2-hydroxyethyl hydrazine (18 μ L, 0.267mmol) and the resulting mixture was heated at 90°C in a sealed Reacti-vial (Trade Mark) for 2 hours. After cooling the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with a solvent gradient of dichloromethane then dichloromethane:methanol (99:1, by volume) to afford the title compound (62mg) as an off-white solid, m.p. 91-93°C.

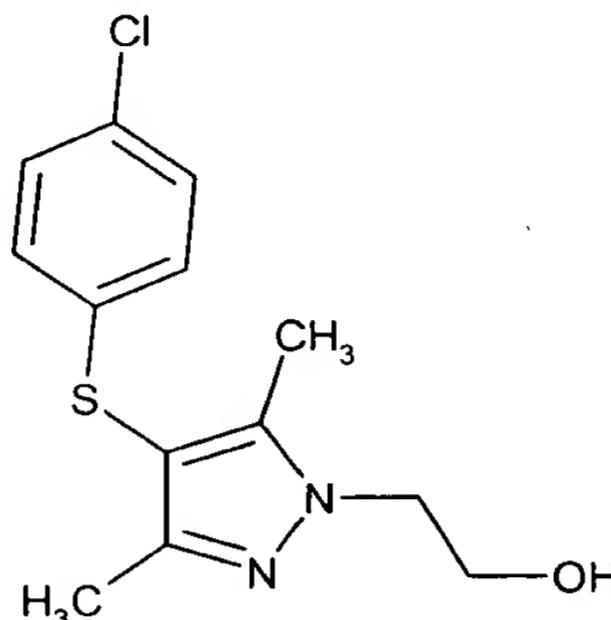
30 $^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 2.13 (s, 3H), 2.61 (m, 1H), 3.80 (s, 2H), 4.05 (m, 2H), 4.17 (m, 2H), 6.92 (s, 2H), 7.16 (s, 1H). This structure was confirmed by nOe experiments.

LRMS (thermospray): m/z [MH $^+$] 353.

Microanalysis: Found: C, 47.66; H, 3.75; N, 7.78. $C_{14}H_{13}Cl_2F_3N_2O$ requires C, 47.61; H, 3.71; N, 7.93%.

EXAMPLE 14

2-{4-[(4-Chlorophenyl)sulfanyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}ethanol



5

The title compound was prepared by a similar method to that of Example 13 using 3-(4-chlorophenylthio)pentane-2,4-dione except that the crude product was purified by recrystallisation from diisopropylether (ca. 25ml) to give pale yellow crystals, m.p. 88.9-90.3°C

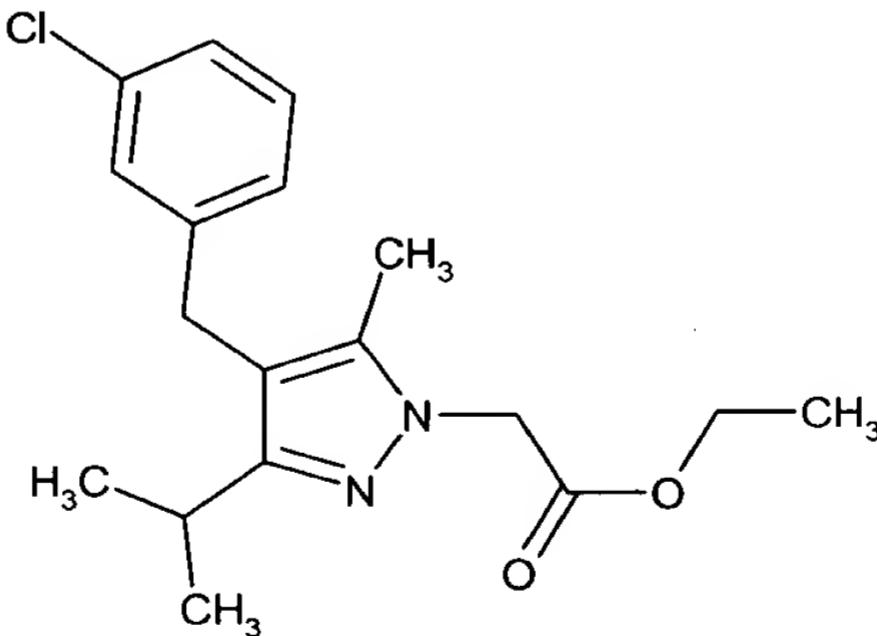
10 1H -NMR 300MHz, $CDCl_3$): δ = 2.20 (s, 3H), 2.29 (s, 3H), 4.04 (t, 2H), 4.12 (t, 2H), 6.90 (d, 2H), 7.18 (d, 2H).

LRMS (thermospray): m/z [MH $^+$] 282.

Microanalysis: Found: C, 54.92; H, 5.39; N, 9.91. $C_{13}H_{15}ClN_2OS$ requires C, 55.22; H, 5.35; N, 9.91%.

EXAMPLE 15

15 Ethyl [4-(3-chlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]acetate



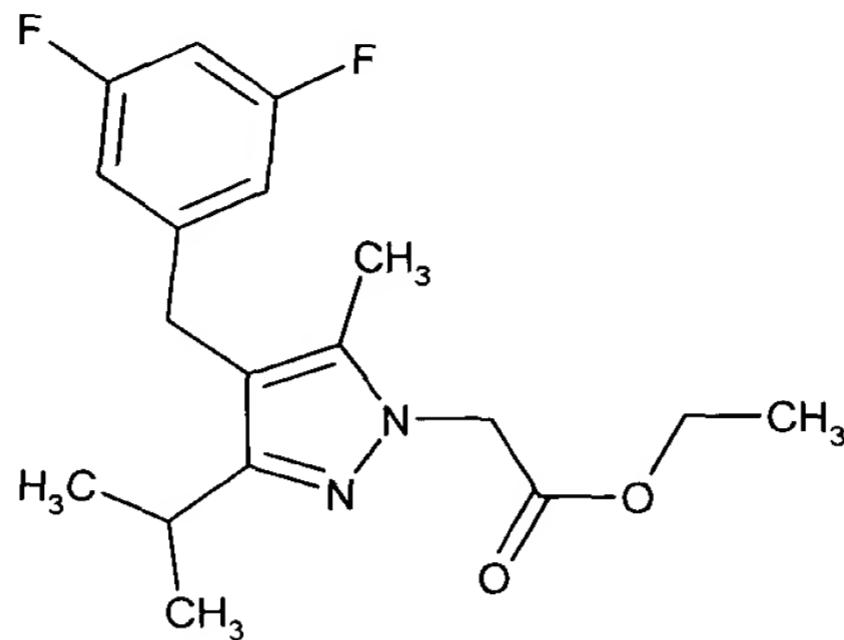
The title compound was prepared by a method similar to that of Example 7, Method A using the pyrazole of Example 20, and was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (5:1, by volume) and was obtained as a colourless oil.

20 1H -NMR (400MHz, $CDCl_3$): δ = 1.13 (d, 6H), 1.26 (t, 3H), 2.03 (s, 3H), 2.79 (m, 1H), 3.72 (s, 2H), 4.19 (q, 2H), 4.81 (s, 2H), 6.93 (m, 1H), 7.03 (s, 1H), 7.11 (m, 2H).

LRMS (thermospray): m/z [MH $^+$] 335.

EXAMPLE 16

Ethyl [4-(3,5-difluorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]acetate



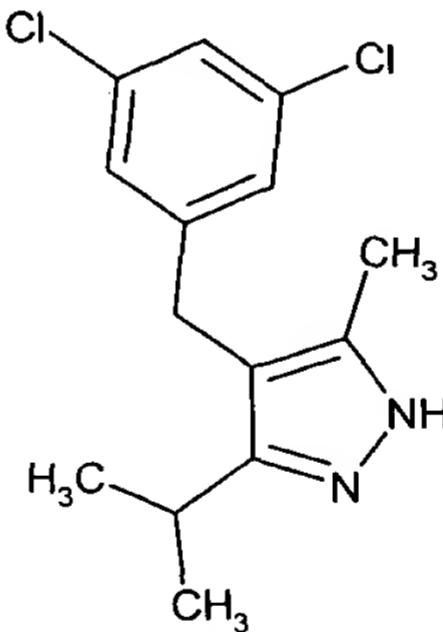
The title compound was prepared by a method similar to that of Example 7, Method A
5 using the pyrazole of Example 18 and was obtained as a yellow oil.

¹H-NMR (400MHz, CDCl₃): δ = 1.16 (d, 6H), 1.27 (t, 3H), 2.06 (s, 3H), 2.82 (heptet,
1H), 3.76 (s, 2H), 4.23 (q, 2H), 4.84 (s, 2H), 6.60 (m, 3H).

HRMS (electrospray): m/z [MH⁺] 337.1719 (calculated 337.1722).

EXAMPLE 17

10 4-(3,5-Dichlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazole



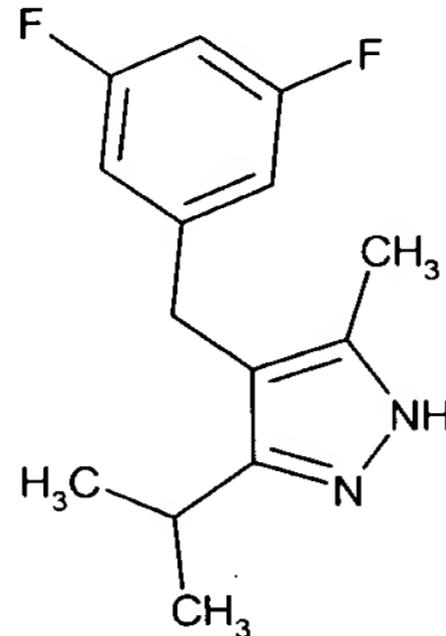
Hydrazine hydrate (50.1mg, 1mmol) was added dropwise to a stirred solution of the
β-diketone of Preparation 1 (287.2mg, 1mmol) in dry ethanol (1ml) in a Reacti-vial (Trade
Mark) at RT. The Reacti-vial (Trade Mark) was sealed and the mixture heated at 80°C for 24
15 hours. After cooling to room temperature the mixture was concentrated under reduced
pressure and the residue purified by flash chromatography on silica gel eluting with a solvent
gradient of pentane:ethyl acetate (3:1, by volume) then pentane:ethyl acetate (2:1, by volume)
to afford the title compound (225.6mg) as a yellow oil.

¹H-NMR (400MHz, CDCl₃): δ = 1.10 (d, 6H), 2.11 (s, 3H), 2.89 (heptet, 1H), 3.74 (s,
20 2H), 6.97 (s, 2H), 7.18 (s, 1H).

LRMS (electrospray): m/z [MH⁺] 285.

EXAMPLE 18

4-(3,5-Difluorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazole



The title compound was prepared by a method similar to that of Example 17 using the
5 β -diketone of Preparation 2 and was purified by flash chromatography on silica gel eluting
with pentane:ethyl acetate (2:1, by volume) to afford the title compound as a yellow oil.

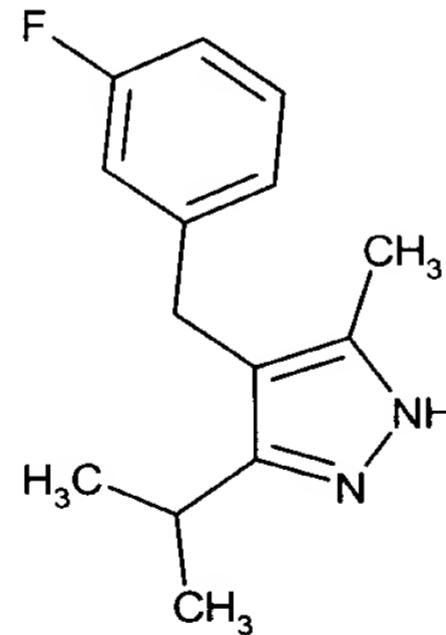
$^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 1.16 (d, 6H), 2.08 (s, 3H), 2.85 (heptet, 1H), 3.71 (s,
2H), 6.58 (m, 3H).

LRMS (thermospray): m/z [MH $^+$] 251.

10

EXAMPLE 19

4-(3-Fluorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazole



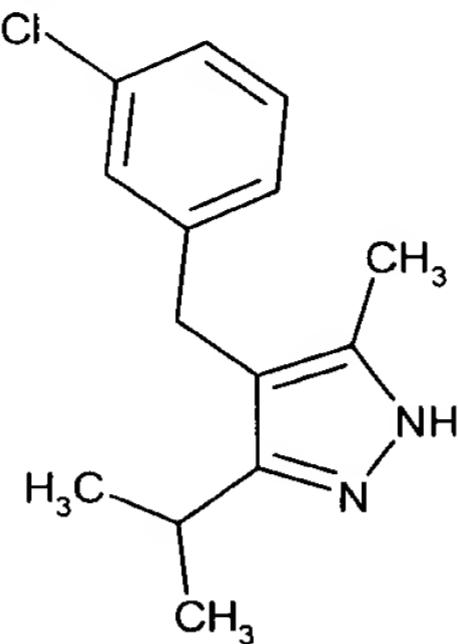
The title compound was prepared by a method similar to that of Example 17 using the
15 β -diketone of Preparation 3 and was purified by flash chromatography on silica gel eluting
with a solvent gradient of pentane:ethyl acetate (3:1, by volume) then pentane:ethyl acetate
(2:1, by volume) to afford the title compound as a yellow oil.

$^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 1.22 (d, 6H), 2.11 (s, 3H), 2.90 (heptet, 1H), 3.77 (s,
2H), 6.77 (d, 1H), 6.89 (m, 2H), 7.20 (m, 1H).

LRMS (thermospray): m/z [MH $^+$] 233.

EXAMPLE 20

4-(3-Chlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazole



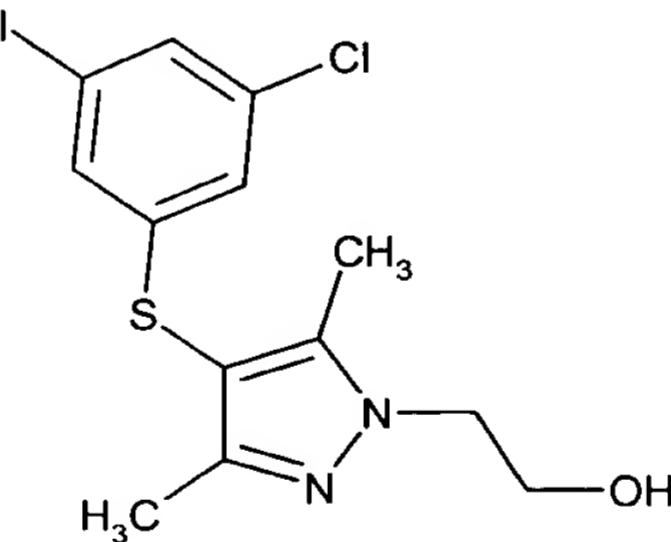
The title compound was prepared by a method similar to that of Example 11 using the
5 β -diketone of Preparation 7 and was purified by flash chromatography on silica gel eluting
with a solvent gradient of pentane:ethyl acetate (5:1, by volume) then pentane:ethyl acetate
(3:1, by volume) to afford the title compound as a colourless oil.

$^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 1.19 (d, 6H), 2.10 (s, 3H), 2.84-2.97 (m, 1H), 3.74 (s,
2H), 6.94-6.99 (m, 1H), 7.06 (s, 1H), 7.11-7.21 (m, 2H).

10 LRMS (thermospray): m/z [MH $^+$] 249.

Example 21

2-{4-[{(3,5-Dichlorophenyl)sulfanyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}ethanol



The β -diketone of Preparation 15 (750mg, 2.71mmol) was added to a stirred solution
15 of 2-hydroxyethyl hydrazine (202 μL , 2.98mmol) in ethanol (27ml) at room temperature under
nitrogen and the resulting yellow solution was heated under reflux for 22 hours. After cooling
the mixture was concentrated under reduced pressure and the resulting pale yellow solid was
purified by flash chromatography on silica gel eluting with methanol:dichloromethane (2:98, by
volume) to provide the title compound (729mg) as a white powder, m.p. 118-120°C.

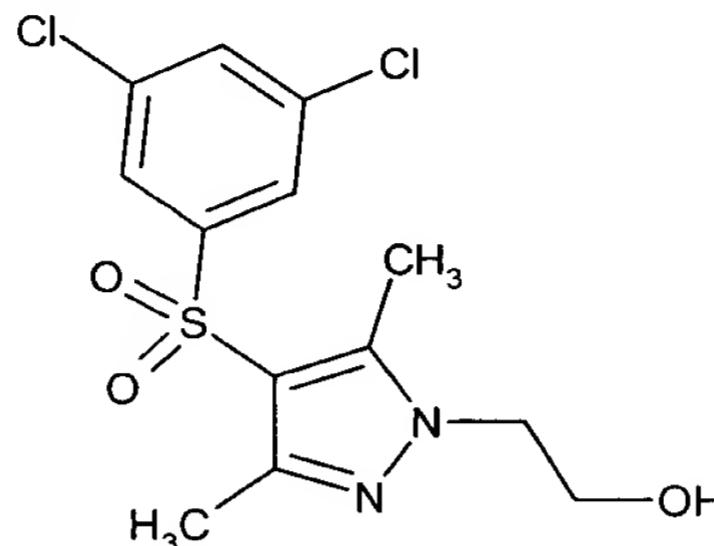
20 $^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 2.18 (s, 3H), 2.24 (s, 3H), 3.19 (t, 1H), 4.01 (m, 2H),
4.12 (m, 2H), 6.78 (s, 2H), 7.02 (s, 1H).

LRMS (thermospray): m/z [MH $^+$] 317.

Microanalysis: Found: C, 49.13; H, 4.45; N, 8.59. $C_{13}H_{14}Cl_2N_2OS$ requires C, 49.22; H, 4.45; N, 8.83%.

Example 22

2-{4-[(3,5-Dichlorophenyl)sulfonyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}ethanol



5

A solution of Oxone (Trade Mark) (581mg, 0.946mmol) in water was added to a stirred suspension of the sulphide of Example 21 (200mg, 0.63mmol) in methanol (2.5ml) at 0°C producing a viscous white suspension. The cooling bath was removed and further methanol (2.5ml) was added to aid dissolution and stirring. The mixture was stirred at room 10 temperature for 2½ hours and at 50°C for 24 hours. After cooling the mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (50ml) and water (25ml). The organic layer was washed with brine (25ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a white solid (195mg). The crude product was pre-absorbed on silica gel and purified by flash 15 chromatography on silica gel eluting with methanol:dichloromethane (2:98, by volume) to provide the title compound (175mg) as a white solid, m.p. 199-200°C.

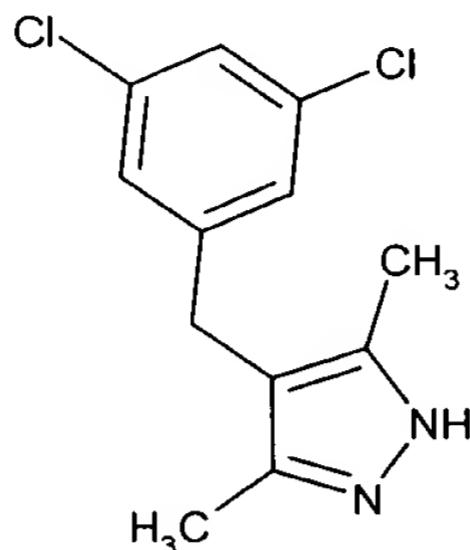
1H -NMR (400MHz, $CDCl_3$): δ = 2.37 (s, 3H), 2.51 (s, 3H), 2.70 (s, 1H), 3.99 (m, 2H), 4.05 (m, 2H), 7.51 (s, 1H), 7.70 (s, 2H).

LRMS (thermospray): m/z [MH $^+$] 349.

20 Microanalysis: Found: C, 44.62; H, 4.03; N, 7.96. $C_{13}H_{14}Cl_2N_2O_3S$ requires C, 44.71; H, 4.04; N, 8.02%.

Example 23

4-(3,5-Dichlorobenzyl)-3,5-dimethyl-1*H*-pyrazole



A stirred suspension of the β -diketone of Preparation 4 (1.01g, 3.90mmol) in ethanol
5 (3ml) was treated with hydrazine hydrate (208 μ L, 4.29mmol) and the resulting mixture was
heated at 100°C in a sealed Reacti-vial (Trade Mark) for 3 hours. After cooling, the mixture
was concentrated under reduced pressure and the residue was purified by flash
chromatography on silica gel eluting with methanol:dichloromethane (2:98, by volume) and
then methanol:dichloromethane (5:95, by volume) to afford the title compound (485mg) as a
10 pale yellow solid, m.p. 133-134°C.

$^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 2.18 (s, 6H), 2.69 (s, 2H), 6.98 (s, 2H), 7.18 (s, 1H).

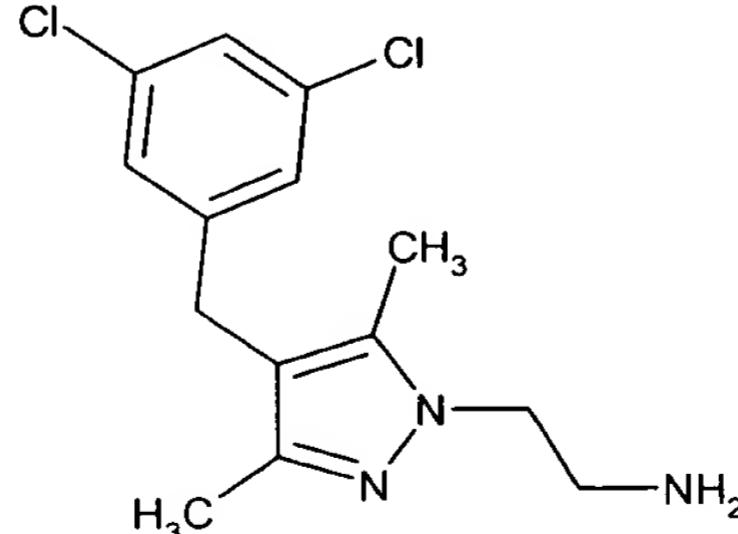
LRMS (electrospray): m/z [MH $^+$] 255.

Microanalysis: Found: C, 56.72; H, 4.79; N, 10.90. $\text{C}_{12}\text{H}_{12}\text{Cl}_2\text{N}_2$ requires C, 56.49; H,
4.74; N, 10.98%.

15 LCMS analysis of the product revealed a small amount (<20%) of dechlorinated
impurities presumably arising from the reduction step in Preparation 4 but not detected at that
stage. This over-reduction could be avoided by using the alternative reduction procedure of
Preparation 6.

Example 24

2-[4-(3,5-Dichlorobenzyl)-3,5-dimethyl-1*H*-pyrazol-1-yl]ethanamine



A stirred suspension of the pyrazole (200mg, 0.78mmol) of Example 23 and 2-chloroethylamine hydrochloride (136mg, 1.18mmol) in toluene (1ml) was heated at 120°C in a sealed Reacti-vial (Trade Mark) for 18 hours. After cooling, the mixture was diluted with

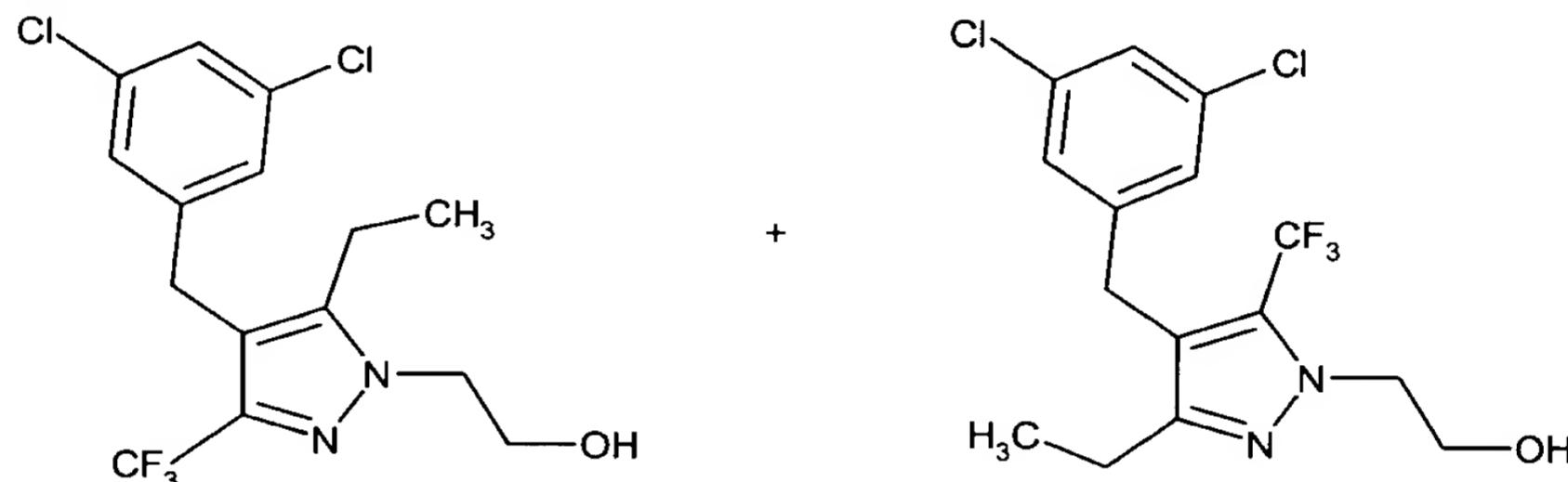
dichloromethane (30ml), washed with 2M aqueous sodium hydroxide solution (20ml), dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with methanol:dichloromethane:ammonia (5:95:0.5, by volume) to afford the title compound 5 (45mg) as white crystals, m.p. 70-72°C.

¹H-NMR (400MHz, CDCl₃): δ = 2.08 (s, 3H), 2.13 (s, 3H), 3.08 (t, 2H), 3.62 (s, 2H), 4.02 (t, 2H), 6.95 (s, 2H), 7.17 (s, 1H).

LRMS (electrospray): m/z [MH⁺] 298.

EXAMPLES 25 and 26

10 2-[4-(3,5-Dichlorobenzyl)-5-ethyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanol (Example 25) and 2-[4-(3,5-Dichlorobenzyl)-3-ethyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanol (Example 26)



A solution of the β-diketone of Preparation 17 (180mg, 0.55mmol) in ethanol (5ml) was treated with 2-hydroxyethyl hydrazine (41µL, 0.61mmol) and heated at 90°C in a sealed Reacti-vial (Trade Mark) for 5 hours. After cooling, the mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with a solvent gradient of methanol:dichloromethane (0:100, by volume) then methanol:dichloromethane (0.5:99.5, by volume). The less polar product to elute from the column was 2-[4-(3,5-Dichlorobenzyl)-5-ethyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanol 20 isolated as a colourless oil (40mg), which solidified on standing, m.p. 70-72°C.

¹H-NMR (300MHz, CDCl₃): δ = 1.03 (t, 3H), 2.60 (q, 2H), 2.90 (t, 1H), 3.87 (s, 2H), 4.13 (m, 2H), 4.20 (m, 2H), 7.00 (s, 2H), 7.20 (s, 1H).

LRMS (thermospray): m/z [MH⁺] 367.

Microanalysis: Found: C, 48.86; H, 4.07; N, 7.45. C₁₅H₁₅Cl₂F₃N₂O requires C, 49.07; H, 4.12; N, 7.43%.

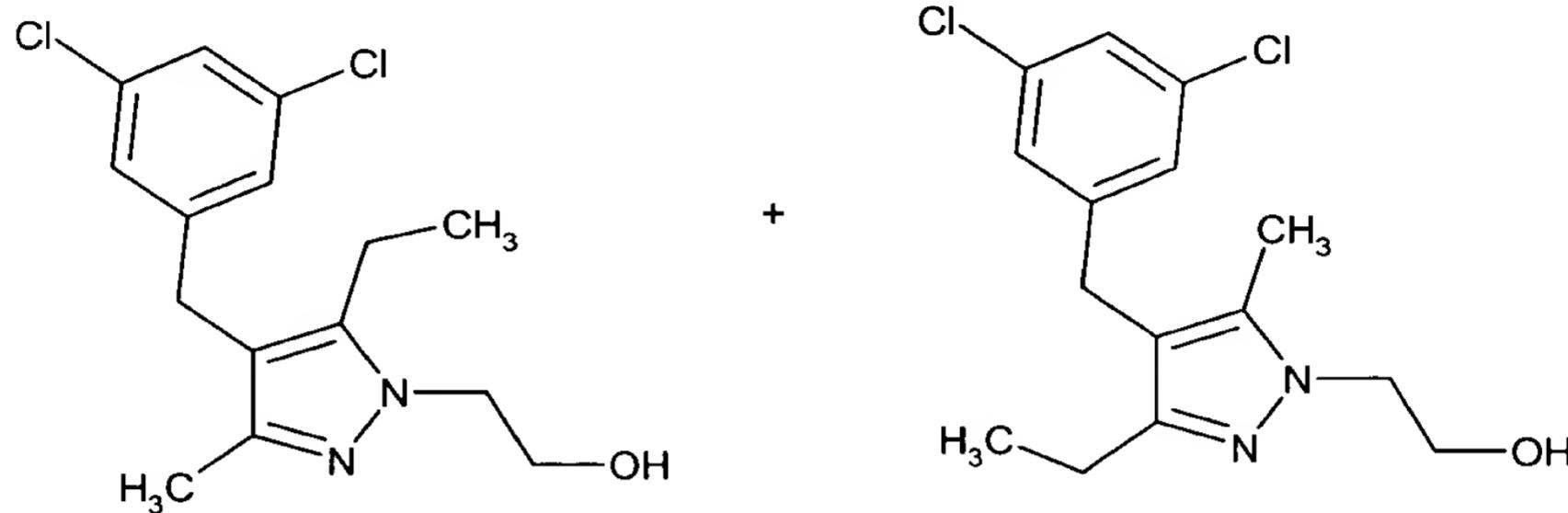
The more polar product to elute from the column was further purified by flash chromatography on silica gel eluting with a solvent gradient of acetonitrile:dichloromethane (5:95, by volume) then acetonitrile:dichloromethane (10:90, by volume). 2-[4-(3,5-Dichlorobenzyl)-3-ethyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanol was isolated as a colourless oil (10mg).

¹H-NMR (300MHz, CDCl₃): δ = 1.17 (t, 3H), 2.52 (q, 2H), 3.48 (brs, 1H), 3.87 (s, 2H), 4.10 (s, 2H), 4.32 (s, 2H), 6.94 (s, 2H), 7.20 (s, 1H).

LRMS (thermospray): m/z [MH⁺] 367.

EXAMPLES 27 and 28

5 2-[4-(3,5-Dichlorobenzyl)-5-ethyl-3-methyl-1*H*-pyrazol-1-yl]ethanol (Example 27) and 2-[4-(3,5-Dichlorobenzyl)-3-ethyl-5-methyl-1*H*-pyrazol-1-yl]ethanol (Example 28)



A solution of the β-diketone of Preparation 20 (300mg, 1.10mmol) in ethanol (5ml) was treated with 2-hydroxyethyl hydrazine (81μL, 1.20mmol) and heated at 90°C for 18 hours. After cooling, the mixture was concentrated under reduced pressure. The two isomers were separated by HPLC (Chiracel OD 25cm x 2cm column; mobile phase, by volume: 80% hexane, 20% iso-propyl alcohol; flow rate: 10 ml/min). The major isomer was isolated as a white solid (60mg, retention time 12.4 minutes), m.p. 106-107°C and shown to be 2-[4-(3,5-dichlorobenzyl)-5-ethyl-3-methyl-1*H*-pyrazol-1-yl]ethanol by nOe experiments.

15 ¹H-NMR (300MHz, CDCl₃): δ = 1.06 (t, 3H), 2.10 (s, 3H), 2.55 (q, 2H), 3.71 (s, 2H), 4.03 (s, 2H), 4.10 (s, 2H), 6.98 (s, 2H), 7.20 (s, 1H).

LRMS (thermospray): m/z [MH⁺] 313.

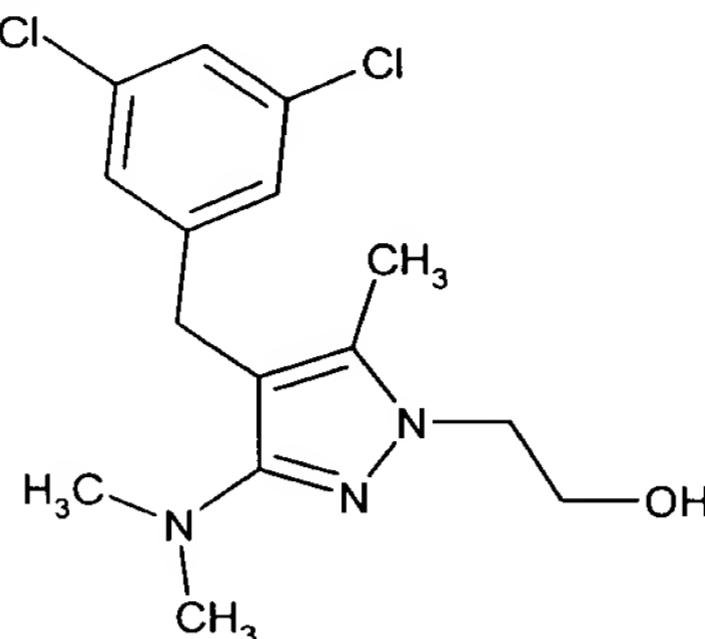
The minor isomer was shown to be 2-[4-(3,5-Dichlorobenzyl)-3-ethyl-5-methyl-1*H*-pyrazol-1-yl]ethanol and isolated as a white solid (10mg, retention time 10.0 minutes), m.p. 20 100-101°C.

¹H-NMR (300MHz, CDCl₃): δ = 1.16 (t, 3H), 2.16 (s, 3H), 2.52 (q, 2H), 3.74 (s, 2H), 4.03 (s, 2H), 4.13 (s, 2H), 6.98 (s, 2H), 7.20 (s, 1H).

LRMS (thermospray): m/z [MH⁺] 313.

Example 29

2-[4-(3,5-Dichlorobenzyl)-3-(dimethylamino)-5-methyl-1*H*-pyrazol-1-yl]ethanol



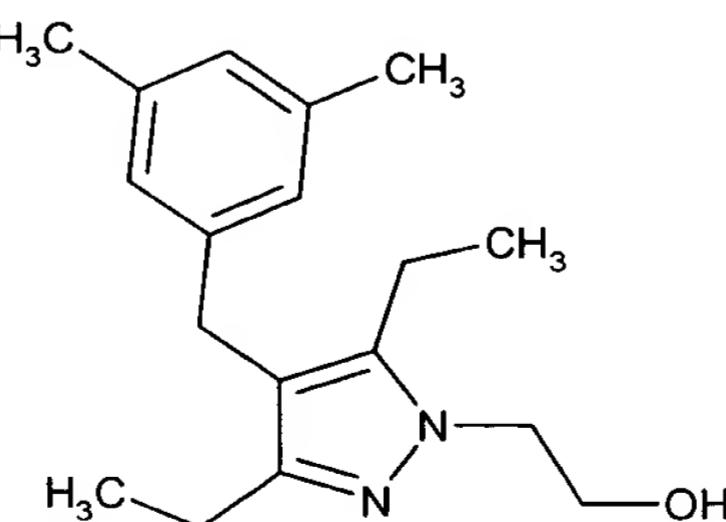
A solution of the amine of Example 87 (18mg, 0.06mmol) in dichloromethane (0.3ml)
5 was treated with triethylamine (8.0 μ L, 0.06mmol) followed by paraformaldehyde (4.0mg,
0.13mmol) and stirred at room temperature for 1 hour. Acetic acid was added (3.5 μ L,
0.06mmol) and after a further hour sodium triacetoxyborohydride (19mg, 0.09mmol) was
added and the reaction mixture was stirred at room temperature for 18 hours. Further
paraformaldehyde (2.2eq) and sodium triacetoxyborohydride (1.5eq) were added and the
10 reaction mixture was stirred at room temperature for 20 hours. The reaction mixture was
diluted with dichloromethane (10ml) and washed with 10% aqueous potassium carbonate
solution (10ml). The organic extract was concentrated under reduced pressure. The crude
material was purified by flash chromatography on silica gel eluting with
dichloromethane:methanol:ammonia (98:2:0.5) to afford the title compound as a colourless oil
15 (4.5mg).

1 H-NMR (300MHz, CDCl₃): δ = 2.08 (s, 3H), 2.70 (s, 6H), 3.78 (s, 2H), 4.00 (s, 4H),
4.19 (m, 1H), 7.02 (s, 2H), 7.20 (s, 1H).

LRMS (thermospray): m/z [MNH₄⁺] 346.

Example 30

20 2-[4-(3,5-Dimethylbenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol

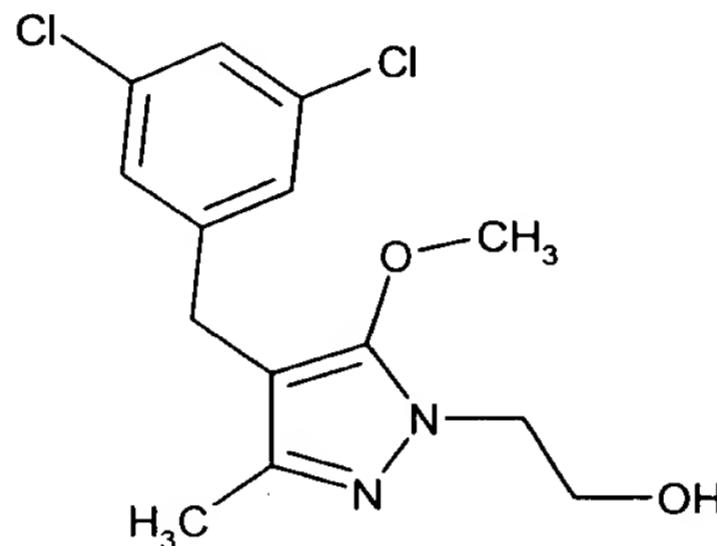


The title compound was prepared by a method similar to that of Example 25, using the β -diketone of Preparation 24. The crude material was purified by flash chromatography on silica gel eluting with methanol:dichloromethane (2:98, by volume) to afford the title compound as a yellow oil, which solidified on standing, m.p. 49.5-51.5°C.

5 $^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 1.03 (t, 3H), 1.16 (t, 3H), 2.29 (s, 6H), 2.55 (m, 4H), 3.71 (s, 2H), 4.03 (m, 2H), 4.13 (m, 2H), 4.35 (brs, 1H), 6.77 (s, 2H), 6.84 (s, 1H).
LRMS (thermospray): m/z [MH $^+$] 287.

Example 31

2-[4-(3,5-Dichlorobenzyl)-5-methoxy-3-methyl-1*H*-pyrazol-1-yl]ethanol



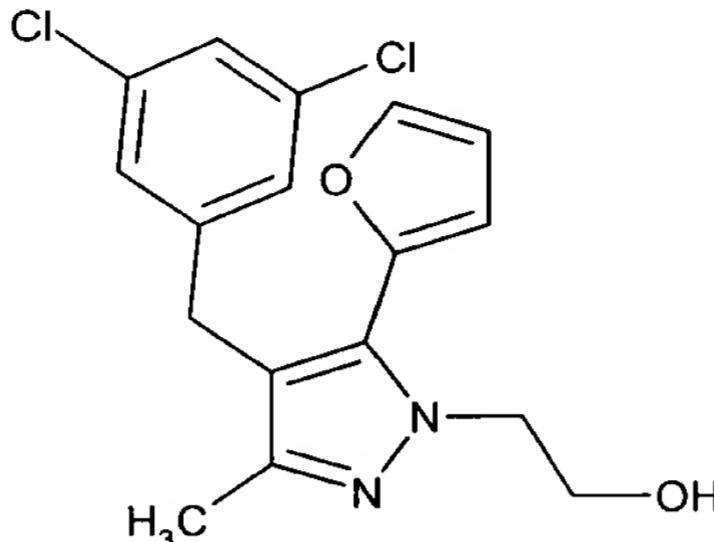
10

A solution of the ester of Example 88 (42mg, 0.12mmol) in tetrahydrofuran (2ml) at 0°C was treated dropwise with a solution of lithiumaluminiumhydride (1M in THF) and the resulting mixture was allowed to warm to room temperature and was stirred at this temperature for a further 30 minutes. The reaction mixture was diluted with ethyl acetate and 15 washed with 1M aqueous sodium hydroxide solution and brine. The organic layer was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to afford the title compound (34mg) as a white solid.

15 $^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 2.07 (s, 3H), 3.45 (brs, 1H), 3.72 (s, 2H), 3.79 (s, 3H), 3.95 (m, 2H), 4.03 (m, 2H), 7.02 (s, 2H), 7.20 (s, 1H).
20 LRMS (thermospray): m/z [MH $^+$] 315.

Example 32

2-[4-(3,5-Dichlorobenzyl)-5-(2-furyl)-3-methyl-1*H*-pyrazol-1-yl]ethanol



A solution of the β -diketone of Preparation 27 (1.0g, 3.20mmol) in ethanol (38ml) was
5 treated with 2-hydroxyethyl hydrazine (239 μ L, 3.53mmol) and heated under reflux for 18 hours. After cooling, the reaction mixture was concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (2:1, by volume) to afford the title compound as a yellow oil, which solidified on standing (703mg).

10 $^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 2.16 (s, 3H), 3.58 (t, 1H), 3.80 (s, 2H), 4.01 (m, 2H), 4.28 (m, 2H), 6.37 (d, 1H), 6.49 (m, 1H), 6.99 (s, 2H), 7.18 (s, 1H), 7.36 (s, 1H).

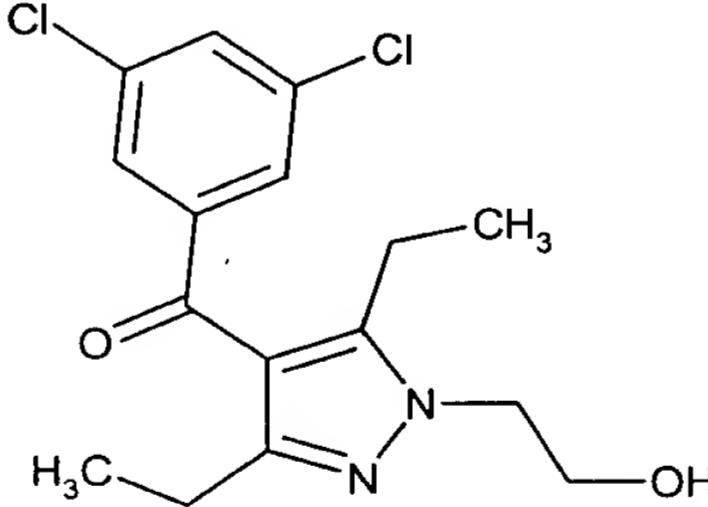
LRMS (thermospray): m/z [MH $^+$] 351.

Microanalysis: Found: C, 58.12; H, 4.63; N, 7.84. $\text{C}_{17}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_2$ requires C, 58.13; H, 4.59; N, 7.98%.

15

Example 33

(3,5-Dichlorophenyl)[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]methanone



A solution of the protected alcohol of Preparation 32 (70mg, 0.15mmol) in tetrahydrofuran (1ml) was treated with tetrabutylammonium fluoride (1M in THF) (300 μ L, 0.30mmol), at room temperature, under a nitrogen atmosphere. After the reaction mixture had been stirred for 18 hours the solution was concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (5:1, by volume) to afford the title compound (30mg) as a white solid, m.p. 133.5-134.4°C.

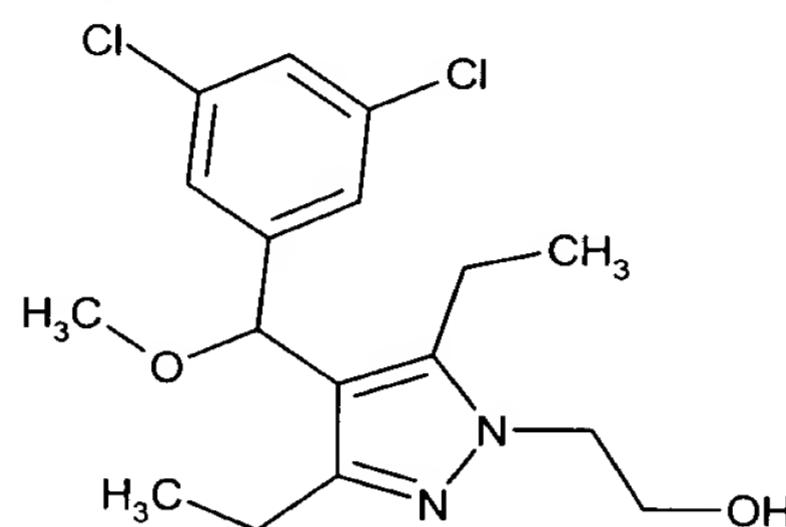
¹H-NMR (300MHz, CDCl₃): δ = 1.13 (m, 6H), 2.52 (q, 2H), 2.74 (q, 2H), 3.65 (t, 1H), 4.10 (m, 2H), 4.19 (m, 2H), 7.61 (m, 3H).

LRMS (thermospray): m/z [MH⁺] 341.

Microanalysis: Found: C, 56.03; H, 5.28; N, 8.13. C₁₆H₁₅Cl₂N₂O₂ requires C, 56.32; H, 5.32; N, 8.21%.

Example 34

(±)-2-{4-[(3,5-Dichlorophenyl)(methoxy)methyl]-3,5-diethyl-1*H*-pyrazol-1-yl}ethanol



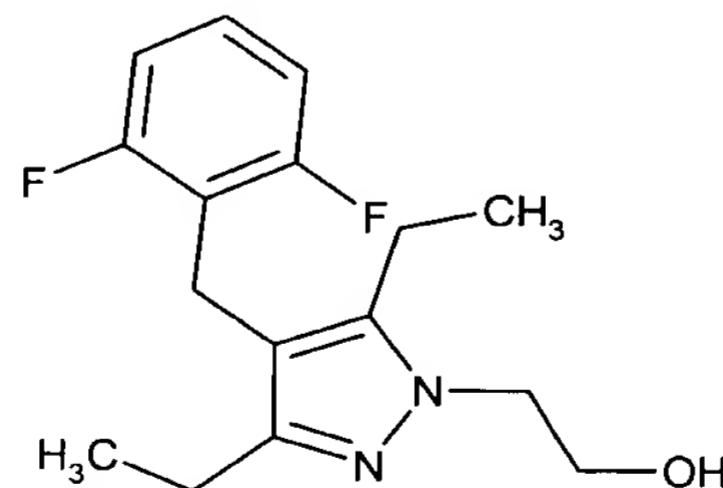
The title compound was prepared by a similar method to that of Example 33 using the protected alcohol of Preparation 33. The crude material was purified by flash chromatography on silica gel eluting with a solvent gradient of cyclohexane:ethyl acetate (5:1, by volume) gradually changing to cyclohexane:ethyl acetate (1:2, by volume) to afford the title compound as a colourless oil.

¹H-NMR (300MHz, CDCl₃): δ = 1.00 (t, 3H), 1.20 (t, 3H), 2.55 (m, 4H), 3.39 (s, 3H), 4.06 (m, 4H), 5.23 (s, 1H), 7.26 (m, 3H).

LRMS (thermospray): m/z [MH⁺] 357.

Example 35

2-[4-(2,6-Difluorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol



A mixture of the β-diketone of Preparation 35 (89mg, 0.35mmol), 2-hydroxyethyl hydrazine (24μL, 0.35mmol) and ethanol (350μL) was heated at 80°C in a sealed Reacti-vial (Trade Mark) for 18 hours. After cooling, the solution was concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (2:1, by volume) to afford the title compound (67mg) as a white solid, m.p. 70-71°C.

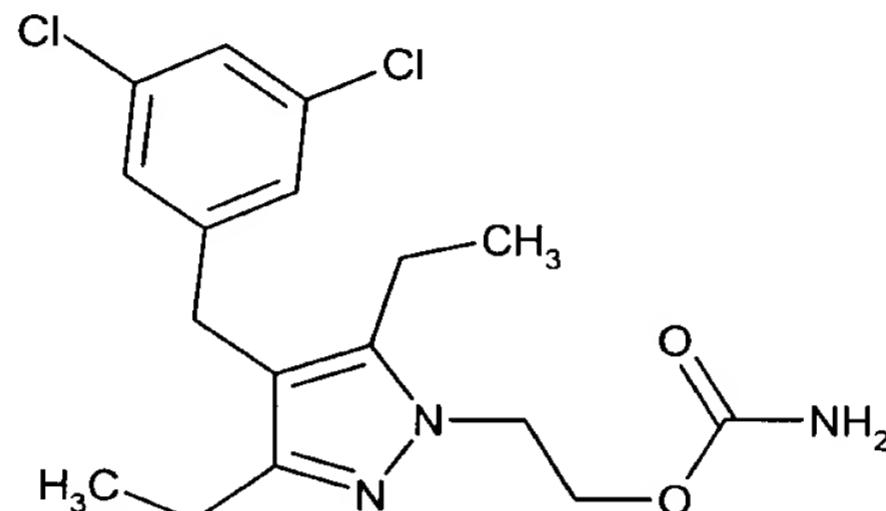
¹H-NMR (400MHz, CDCl₃): δ = 1.00 (t, 3H), 1.15 (t, 3H), 2.55 (q, 2H), 2.62 (q, 2H), 3.73 (s, 2H), 3.97 (m, 2H), 4.00 (m, 2H), 4.26 (t, 1H), 6.84 (t, 2H), 7.15 (m, 1H).

LRMS (electrospray): m/z [MH⁺] 295.

5 Microanalysis: Found: C, 65.20; H, 6.87; N, 9.48. C₁₆H₂₀F₂N₂O requires C, 65.29; H, 6.85; N, 9.52%.

Example 36

2-[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl carbamate



10 A solution of the alcohol of Example 2 (50mg, 0.15mmol) in dichloromethane (1.5ml) was cooled to 0°C and treated dropwise with trichloroacetyl isocyanate (22μL, 0.18mmol) under a nitrogen atmosphere. After stirring at 0°C for 1.5 hours the solution was concentrated under reduced pressure. The residue was dissolved in methanol (1ml) and water (0.5ml) and cooled to 0°C. Potassium carbonate (64mg, 0.46mmol) was added and the resulting mixture 15 was stirred at this temperature for 1 hour. The reaction mixture was allowed to warm to room temperature and stirred for 18 hours. The solution was concentrated under reduced pressure. The residue was partitioned between dichloromethane and water. The organic extract was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel 20 eluting with dichloromethane:methanol (98:2, by volume) to afford the title compound (42mg) as a white solid, m.p. 145-147°C.

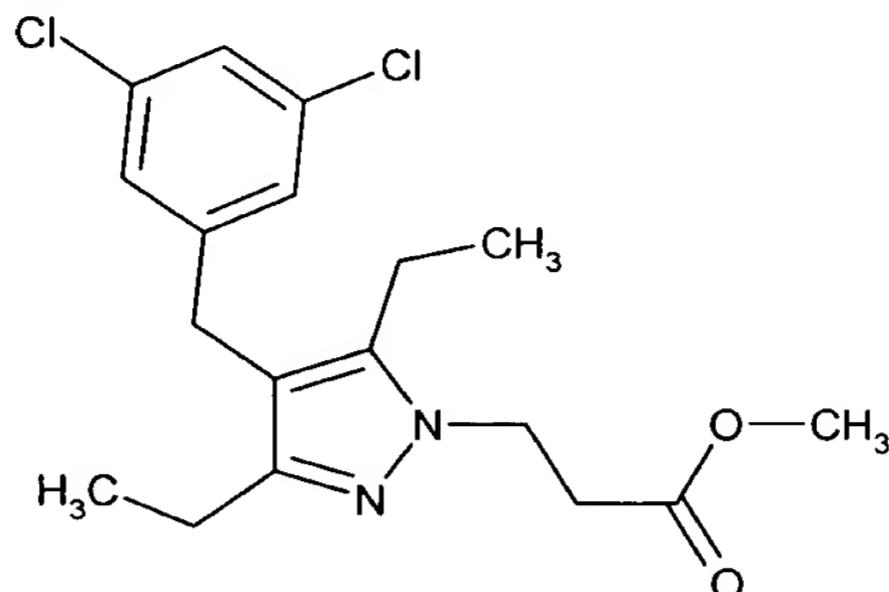
¹H-NMR (400MHz, CDCl₃): δ = 1.02 (t, 3H), 1.10 (t, 3H), 2.42 (m, 2H), 2.50 (m, 2H), 3.68 (s, 2H), 4.21 (t, 2H), 4.42 (t, 2H), 4.55 (brs, 2H), 6.94 (s, 2H), 7.15 (s, 1H).

LRMS (thermospray): m/z [MH⁺] 370.

25 Microanalysis: Found: C, 54.95; H, 5.65; N, 11.20. C₁₇H₂₁Cl₂N₃O₂ requires C, 55.14; H, 5.72; N, 11.35%.

EXAMPLES 37 and 38

Methyl 3-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]propanoate (Example 37)



A solution of the pyrazole of Example 11 (198mg, 0.70mmol) in ethanol (1ml) was
5 treated with sodium ethoxide (21% w/v in EtOH) (261 μ L, 0.81mmol) and then methyl-3-
bromopropionate (153 μ L, 1.40mmol) and heated at 70°C in a sealed Reacti-vial (Trade Mark)
for 18 hours. Over a period of 3 days more sodium ethoxide (2.65eq) and methyl-3-
bromopropionate (6.0eq) were added and the reaction was maintained under the same
conditions. After cooling, the solution was concentrated under reduced pressure. The
10 residue was partitioned between dichloromethane and water. The organic phase was dried
over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The
crude material was purified by flash chromatography on silica gel eluting with pentane:ethyl
acetate (5:1, by volume) to afford two products.

The first compound eluted off the column was ethyl 3-[4-(3,5-dichlorobenzyl)-3,5-
15 diethyl-1*H*-pyrazol-1-yl]propanoate (Example 38) isolated as a pale yellow oil (150mg).

$^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 1.06 (t, 3H), 1.13 (t, 3H), 1.26 (t, 3H), 2.47 (q, 2H),
2.56 (q, 2H), 2.94 (t, 2H), 3.71 (s, 2H), 4.15 (q, 2H), 4.29 (t, 2H), 6.98 (s, 2H), 7.20 (s, 1H).

LRMS (thermospray): m/z [MH $^+$] 383.

Accurate Mass: Found: 383.1284 [MH $^+$]; $\text{C}_{19}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}_2$ requires 383.1288 [MH $^+$].

20 The second compound eluted was Example 37 (21mg) isolated as a colourless oil.

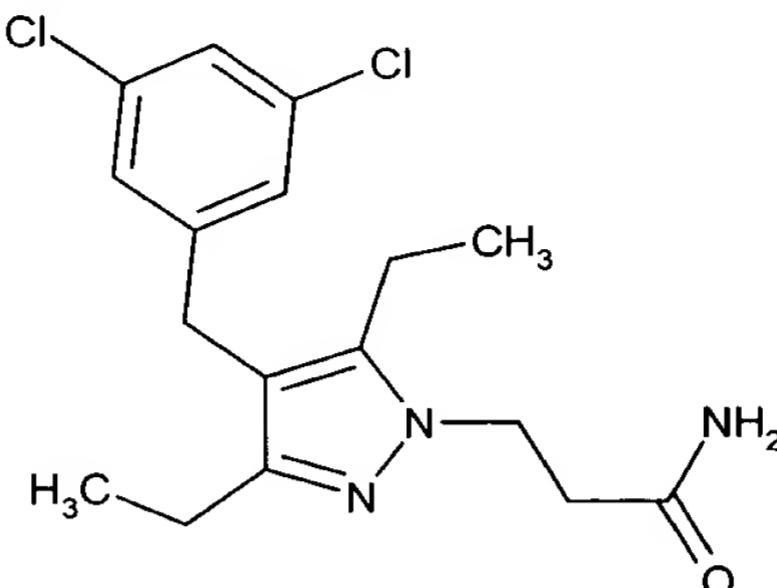
$^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 1.06 (t, 3H), 1.15 (t, 3H), 2.47 (q, 2H), 2.56 (q, 2H),
2.97 (t, 2H), 3.71 (s, 5H), 4.31 (t, 2H), 6.97 (s, 2H), 7.20 (s, 1H).

LRMS (thermospray): m/z [MH $^+$] 369.

Accurate Mass: Found: 369.1128 [MH $^+$]; $\text{C}_{18}\text{H}_{22}\text{Cl}_2\text{N}_2\text{O}_2$ requires 369.1131 [MH $^+$].

Example 39

3-[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]propanamide



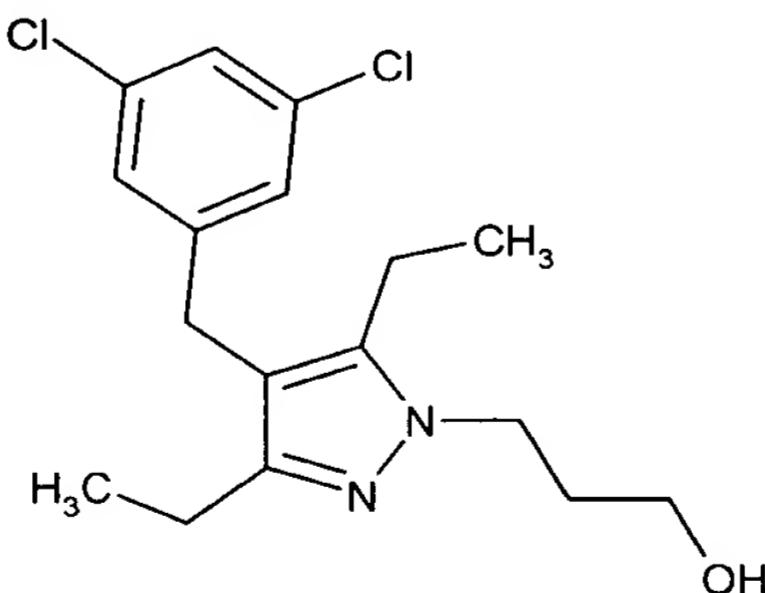
A solution of the ethyl ester of Example 38 (60mg, 0.16mmol) in a saturated solution
5 of ammonia in methanol (1.2ml) was heated at 90°C in a sealed Reacti-vial (Trade Mark) for
18 hours. Further saturated ammonia in methanol (1.0ml) was added and the reaction
mixture was stirred at 90°C for 3 days. After cooling, the solution was concentrated under
reduced pressure. The crude material was purified by flash chromatography on silica gel
eluting with ethyl acetate to afford the title compound (50mg) as a white solid, m.p. 140-
10 142°C.

¹H-NMR (400MHz, CDCl₃): δ = 1.00 (t, 3H), 1.08 (t, 3H), 2.40 (q, 2H), 2.52 (q, 2H),
2.80 (t, 2H), 3.66 (s, 2H), 4.26 (t, 2H), 5.26 (brs, 1H), 6.29 (brs, 1H), 6.92 (s, 2H), 7.15 (s, 1H).
LRMS (electrospray): m/z [MH⁺] 354.

Microanalysis: Found: C, 57.51; H, 6.01; N, 11.57. C₁₇H₂₁Cl₂N₃O requires C, 57.63;
15 H, 5.97; N, 11.86%.

Example 40

3-[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]-1-propanol



A solution of the ethyl ester of Example 38 (60mg, 0.16mmol) in diethyl ether (2ml)
20 was cooled to -78°C, treated dropwise with lithium aluminium hydride (1M in THF) (170μL,
0.17mmol) and stirred at -78°C, under a nitrogen atmosphere for 30 minutes. The reaction
mixture was allowed to warm to 0°C and stirred at this temperature for 1 hour. The reaction
was quenched with a few drops of water. The reaction mixture was partitioned between

diethyl ether and dilute aqueous hydrochloric acid. The organic phase was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (1:1, by volume) to afford the title compound (39mg) as a white solid, m.p. 56-59°C.

5 ¹H-NMR (300MHz, CDCl₃): δ = 1.05 (t, 3H), 1.16 (t, 3H), 2.02 (m, 2H), 2.47 (q, 2H), 2.53 (q, 2H), 3.69 (m, 4H), 4.06 (brs, 1H), 4.20 (t, 2H), 6.97 (s, 2H), 7.20 (s, 1H).

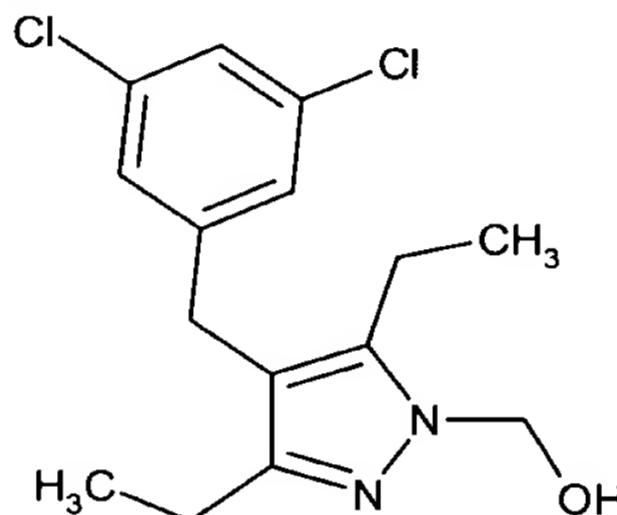
LRMS (thermospray): m/z [MH⁺] 341.

Microanalysis: Found: C, 59.86; H, 6.54; N, 8.14. C₁₇H₂₂Cl₂N₂O requires C, 59.83; H, 6.50; N, 8.21%.

10

Example 41

[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]methanol



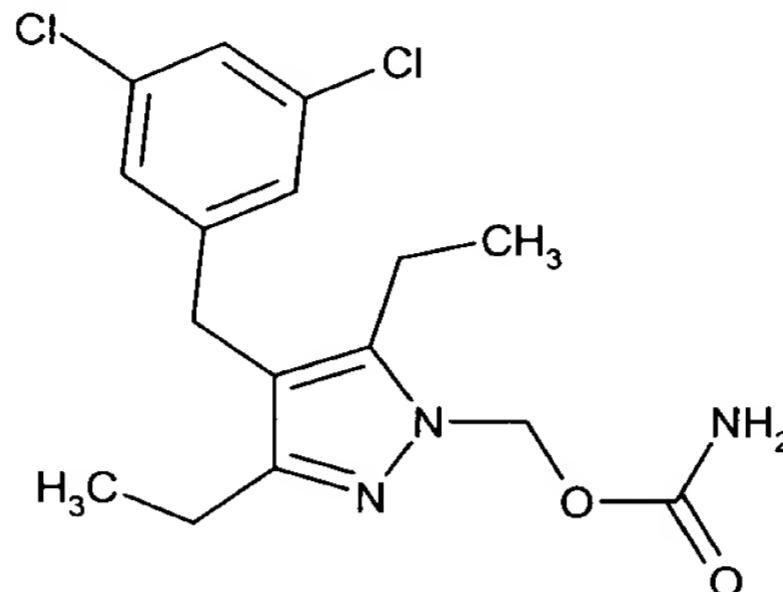
A solution of the pyrazole of Example 11 (283mg, 1.00mmol) in water (1ml) and ethanol (0.5ml) was treated with 37%^{w/w} aqueous formaldehyde solution (112μL, 1.50mmol) 15 and the resulting mixture was stirred at room temperature for 18 hours. The reaction was then stirred under reflux for 2 hours. The reaction mixture was diluted with water and extracted with dichloromethane. The organic extract was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (2:1, by volume) to afford the title compound (231mg) as a white solid, m.p. 117-118°C.

20 ¹H-NMR (300MHz, CDCl₃): δ = 1.16 (m, 6H), 2.48 (q, 2H), 2.65 (q, 2H), 3.73 (s, 2H), 5.50 (s, 2H), 5.80 (brs, 1H), 7.00 (s, 2H), 7.20 (s, 1H).

Microanalysis: Found: C, 57.48; H, 5.78; N, 8.87. C₁₅H₁₈Cl₂N₂O requires C, 57.52; H, 5.79; N, 8.94%.

Example 42

[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]methyl carbamate



A solution of the alcohol of Example 41 (280mg, 0.90mmol) in dichloromethane (5ml)
5 was cooled to 0°C, treated with trichloroacetyl isocyanate (128µl, 1.1mmol) and stirred at 0°C
for 30 minutes. The solution was soaked into a pad of alumina (neutral, activity II,
Brockmann), washed with dichloromethane and then extracted with ethyl acetate. The
organic extract was concentrated under reduced pressure. The crude material was purified by
flash chromatography on silica gel eluting with a solvent gradient of cyclohexane:ethyl acetate
10 (2:1, by volume) gradually changing to cyclohexane:ethyl acetate (1:1, by volume) to afford
the title compound (238mg) as a solid, m.p. 153-155°C.

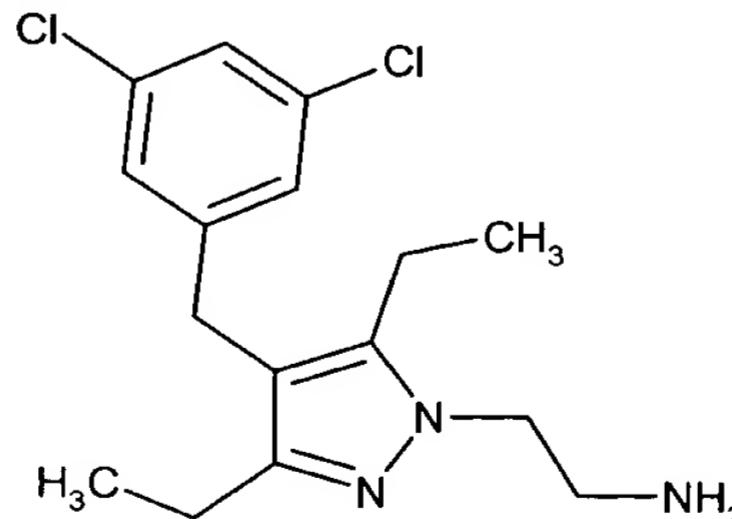
¹H-NMR (400MHz, CDCl₃): δ = 1.03 (t, 3H), 1.11 (t, 3H), 2.42 (q, 2H), 2.60 (q, 2H),
3.66 (s, 2H), 4.66 (brs, 2H), 5.94 (s, 2H), 6.92 (s, 2H), 7.13 (s, 1H).

LRMS (thermospray): m/z [MH⁺] 356.

15 Microanalysis: Found: C, 54.04; H, 5.39; N, 11.65. C₁₆H₁₉Cl₂N₃O₂ requires C, 53.94;
H, 5.38; N, 11.79%.

Example 43

2-[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanamine



20 The pyrazole of Example 11 (5.47g, 19.3mmol) was mixed with 2-chloroethylamine
hydrochloride (2.46g, 21.3mmol) and heated neat at 150°C for 20 hours. After cooling, the
solid was partitioned between dichloromethane and 10% aqueous potassium carbonate
solution. The organic extract was concentrated under reduced pressure. The crude material
was purified by flash chromatography on silica gel eluting with a solvent gradient of

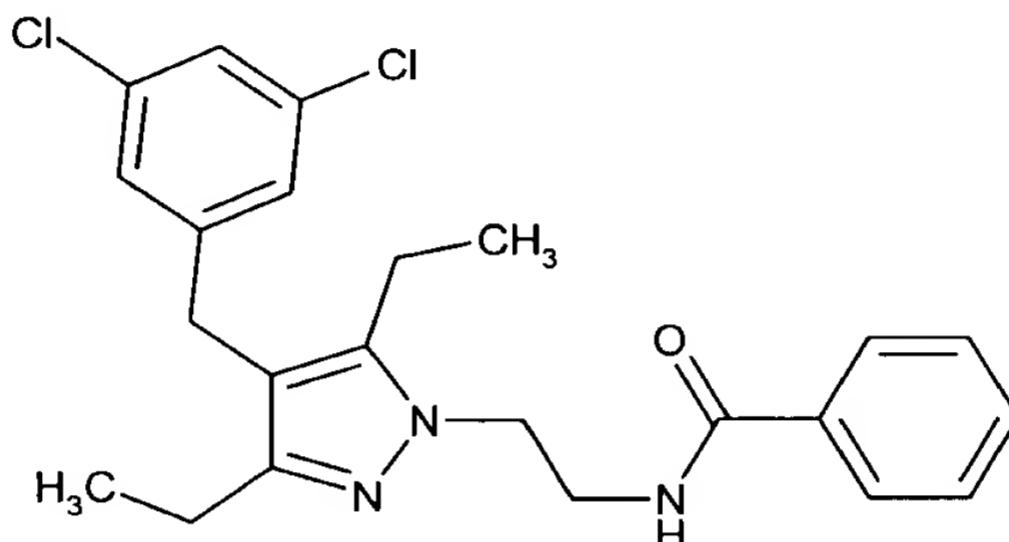
dichloromethane:methanol:ammonia (95:5:0, by volume) gradually changing to dichloromethane:methanol:ammonia (90:10:1, by volume) to afford the title compound (3.37g) as a colourless oil.

5 $^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 1.03 (t, 3H), 1.15 (t, 3H), 2.45 (q, 2H), 2.52 (q, 2H),
3.16 (t, 2H), 3.71 (s, 2H), 4.06 (t, 2H), 6.97 (s, 2H), 7.18 (s, 1H).

LRMS (thermospray): m/z [MH $^+$] 326

Example 44

N{2-[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}benzamide



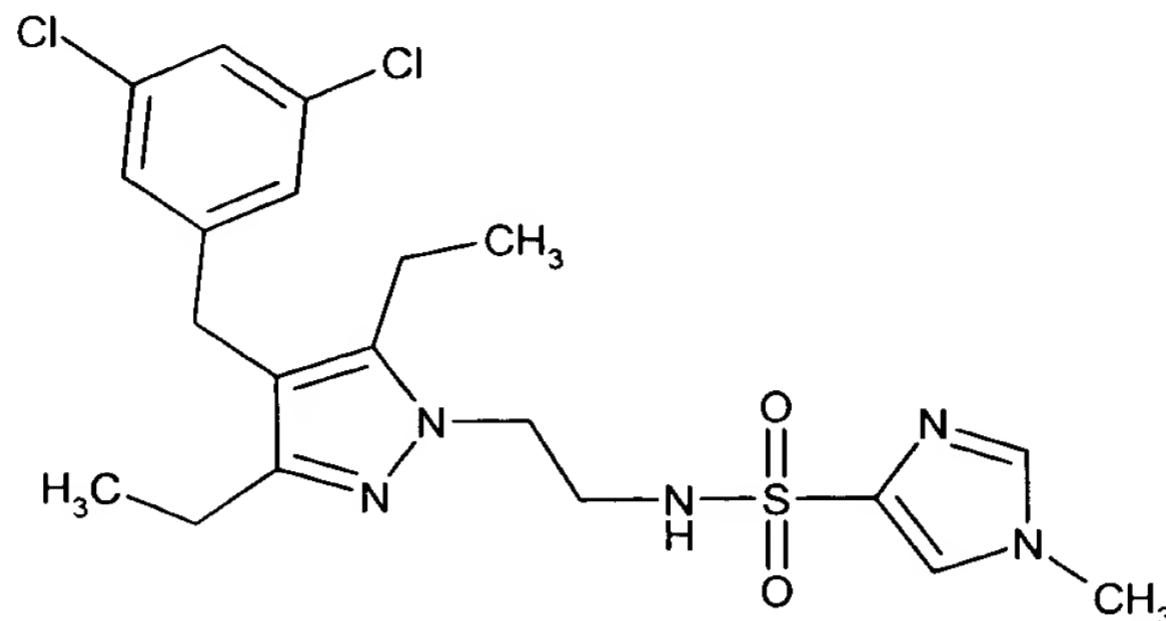
10 A solution of the amine of Example 43 (98mg, 0.30mmol) in dimethylformamide (3.75ml) was treated with benzoic acid (41mg, 0.33mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (64mg, 0.33mmol) and 4-dimethylaminopyridine (81mg, 0.66mmol) and stirred at room temperature for 18 hours. The solution was concentrated under reduced pressure. The residue was partitioned between dichloromethane and
15 saturated sodium hydrogen carbonate solution. The organic extract was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (95:5, by volume) to afford the title compound (48mg) as a white solid, m.p. 115-117°C.

15 $^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 1.03 (t, 3H), 1.20 (t, 3H), 2.48 (q, 2H), 2.55 (q, 2H),
3.68 (s, 2H), 3.89 (m, 2H), 4.23 (t, 2H), 6.97 (s, 2H), 7.18 (s, 1H), 7.42 (m, 2H), 7.48 (m, 1H),
7.60 (brs, 1H), 7.80 (d, 2H).

LRMS (thermospray): m/z [MH $^+$] 430.

Example 45

N-{2-[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-1-methyl-1*H*-imidazole-4-sulfonamide



5 A solution of the amine of Example 43 (98mg, 0.30mmol) in dimethylformamide (3.75ml) was treated with 1-methylimidazole-4-sulphonyl chloride (60mg, 0.33mmol) and triethylamine (46 μ L, 0.33mmol) and the resulting mixture was stirred at room temperature for 18 hours. The solution was concentrated under reduced pressure. The residue was partitioned between dichloromethane and saturated aqueous sodium hydrogencarbonate solution. The organic extract was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (95:5, by volume) to afford the title compound (55mg) as a white solid, m.p. 172-174°C.

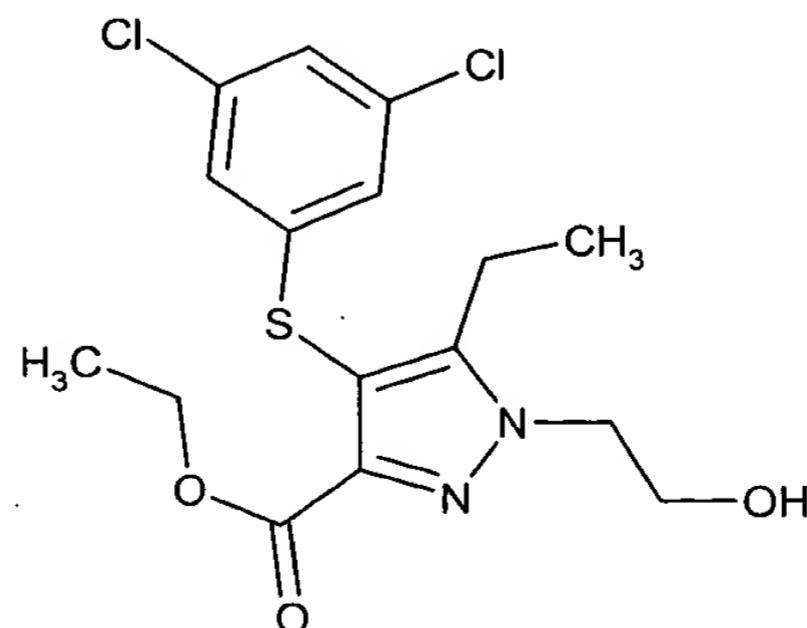
10

15 $^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 1.00 (t, 3H), 1.08 (t, 3H), 2.40 (q, 2H), 2.50 (q, 2H), 3.52 (m, 2H), 3.66 (s, 2H), 3.71 (s, 3H), 4.15 (m, 2H), 6.06 (t, 1H), 6.95 (s, 2H), 7.16 (s, 1H).
LRMS (electrospray): m/z [MH $^+$] 470.

EXAMPLES 46 and 47

Ethyl 4-[(3,5-dichlorophenyl)sulfanyl]-5-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazole-3-carboxylate

20 (Example 46)



To a stirred suspension of the β -diketone of Preparation 36 (664mg, 1.90mmol) in ethanol (1.3ml) was added 2-hydroxyethyl hydrazine (145mg, 1.90mmol) and the resulting mixture was heated at 80°C in a sealed Reacti-vial (Trade Mark) for 3 hours. After cooling, the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (3:1, by volume) and then pentane:ethyl acetate (1:1, by volume) to afford two compounds.

The more polar material was Example 46 (587mg) isolated as a pale yellow oil.

$^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 1.13 (t, 3H), 1.25 (t, 3H), 2.82 (q, 2H), 4.12 (q, 2H), 4.35 (m, 4H), 6.89 (s, 2H), 7.00 (s, 1H).

10 LRMS (electrospray): m/z [MNa $^+$] 411.

The less polar material was ethyl 4-[(3,5-dichlorophenyl)sulfanyl]-3-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazole-5-carboxylate (Example 47) (40mg) isolated as a colourless oil.

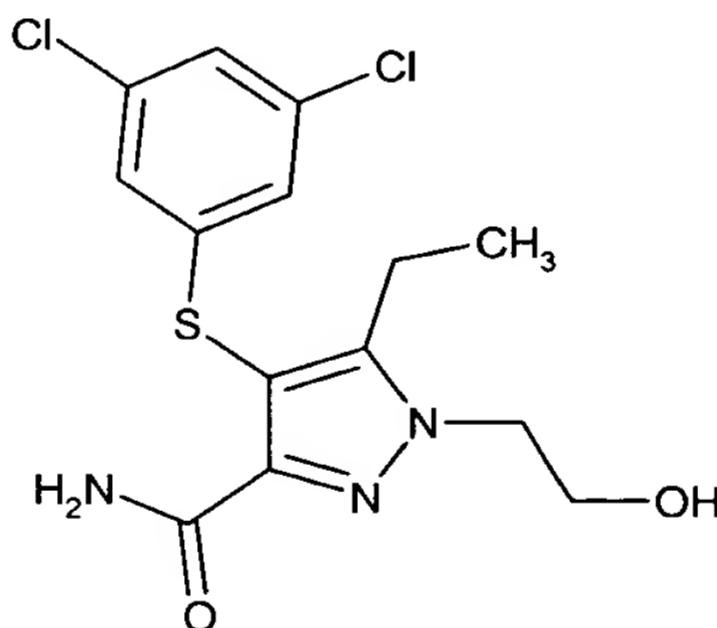
$^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 1.15 (m, 6H), 2.61 (q, 2H), 4.03 (m, 2H), 4.04 (q, 2H), 4.64 (t, 2H), 6.83 (s, 2H), 7.03 (s, 1H).

15 LRMS (electrospray): m/z [MH $^+$] 389.

Accurate Mass: Found 389.0481 [MH $^+$]; $\text{C}_{16}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_3\text{S}$ requires 389.0488 [MH $^+$].

Example 48

4-[(3,5-Dichlorophenyl)sulfanyl]-5-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazole-3-carboxamide



20 A mixture of Example 46 (407mg, 1.05mmol) and 0.880 ammonia solution was heated at 90°C in a sealed Reacti-vial (Trade Mark) for 18 hours. The precipitate was filtered off and washed with water (5ml) to afford the title compound (273mg) as a white solid, m.p. 214-216°C.

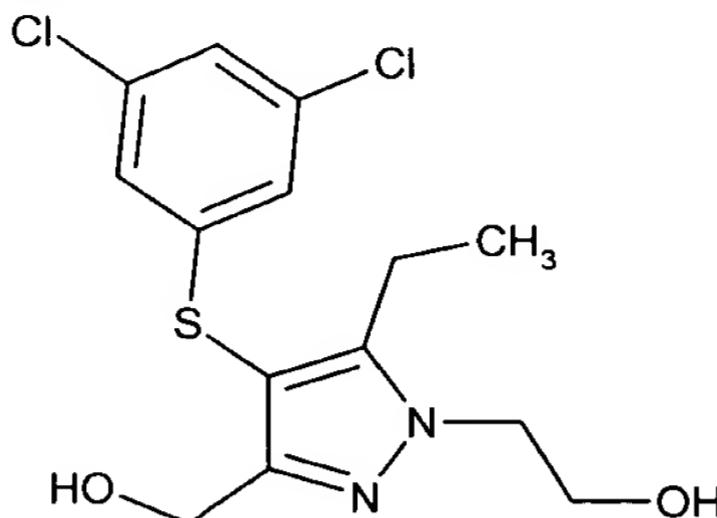
25 $^1\text{H-NMR}$ (300MHz, CD_3OD): δ = 1.13 (t, 3H), 2.82 (q, 2H), 4.01 (t, 2H), 4.32 (t, 2H), 6.99 (s, 2H), 7.19 (s, 1H).

LRMS (thermospray): m/z [MNa $^+$] 382.

Microanalysis: Found: C, 46.59; H, 4.10; N, 11.23. $\text{C}_{14}\text{H}_{15}\text{Cl}_2\text{N}_3\text{O}_2\text{S}$ requires C, 46.68; H, 4.20; N, 11.66%.

Example 49

2-[4-[(3,5-Dichlorophenyl)sulfanyl]-5-ethyl-3-(hydroxymethyl)-1*H*-pyrazol-1-yl]ethanol



A solution of Example 46 (65mg, 0.17mmol) in tetrahydrofuran (2.5ml) was cooled to
5 -78°C and treated with lithiumaluminium hydride (1M in THF) (170µL, 0.17mmol). After
stirring at -78°C for 2 hours the reaction mixture was allowed to warm to 0°C for 1 hour and
was then allowed to warm to room temperature. After stirring at this temperature for 18
hours, water (1ml) was added. The reaction mixture was partitioned between ethyl acetate
10 (25ml) and water (25ml). The organic phase was dried over anhydrous magnesium sulphate,
filtered and concentrated under reduced pressure. The crude material was purified by flash
chromatography on silica gel eluting with dichloromethane:methanol (95:5, by volume) to
afford the title compound (42mg) as a colourless oil, which solidified on standing, m.p. 89-
90°C.

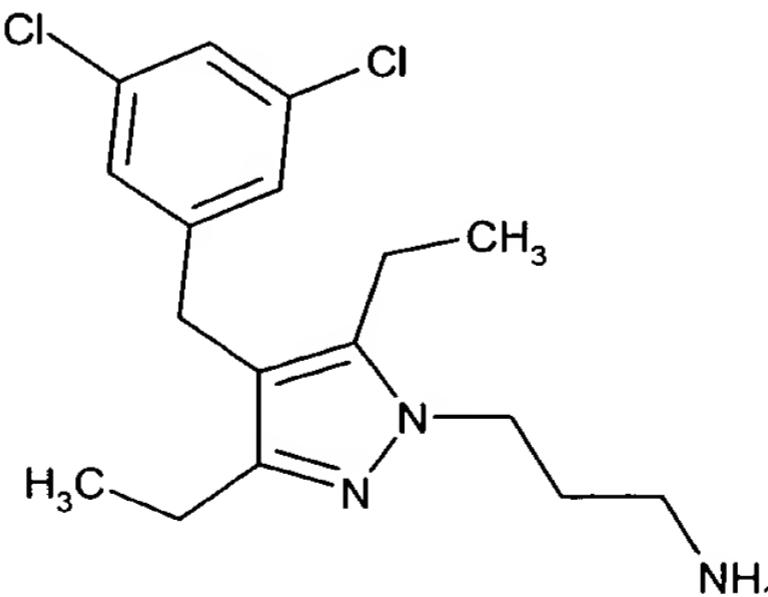
1H-NMR (400MHz, CDCl3): δ = 1.06 (t, 3H), 2.09 (brs, 1H), 2.67 (q, 2H), 3.13 (brs,
15 1H), 4.03 (m, 2H), 4.18 (t, 2H), 4.60 (m, 2H), 6.92 (s, 2H), 7.03 (s, 1H).

LRMS (electrospray): m/z [MNa⁺] 369.

Accurate Mass: Found 347.0383 [MH⁺]; C₁₄H₁₆Cl₂N₂O₂S requires 347.0383 [MH⁺].

Example 50

3-[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]-1-propanamine



20

The pyrazole of Example 11 (200mg, 0.71mmol) was mixed with 3-chloropropylamine hydrochloride (138mg, 1.06mmol). The resulting mixture was heated neat at 150°C, for 24 hours, under a nitrogen atmosphere. After cooling, the reaction mixture was partitioned between dichloromethane (30ml) and saturated aqueous sodium hydrogencarbonate solution

(30ml). The organic phase was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol:ammonia (90:10:0, by volume) gradually changing to 5 dichloromethane:methanol:ammonia (90:10:1, by volume) to afford the title compound (203mg) as a brown oil.

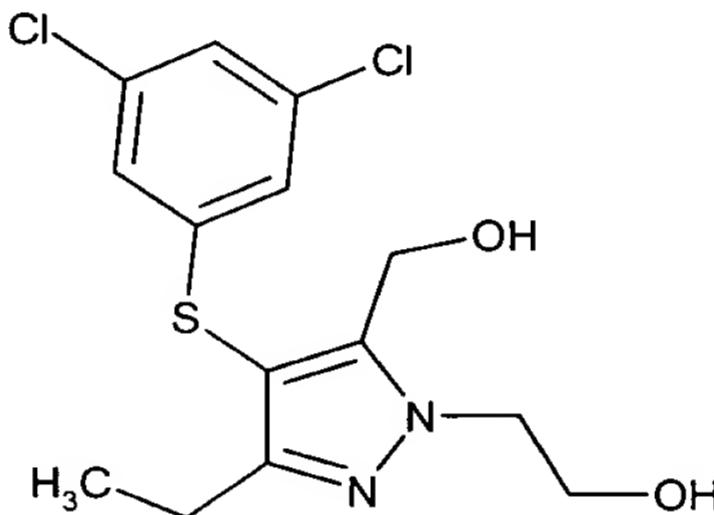
¹H-NMR (400MHz, CDCl₃): δ = 1.04 (t, 3H), 1.13 (t, 3H), 1.96 (m, 2H), 2.45 (q, 2H), 2.50 (q, 2H), 2.78 (t, 2H), 3.69 (s, 2H), 4.09 (t, 2H), 6.99 (s, 2H), 7.19 (s, 1H).

LRMS (electrospray): m/z [MH⁺] 342.

10

Example 51

2-[4-[(3,5-Dichlorophenyl)sulfanyl]-3-ethyl-5-(hydroxymethyl)-1*H*-pyrazol-1-yl]ethanol



The title compound was prepared by a similar method to that of Example 49 using Example 47 except that the crude material was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (1:1, by volume) to afford the title compound as a white solid, m.p. 106-108°C.

¹H-NMR (300MHz, CDCl₃): δ = 1.20 (t, 3H), 2.61 (q, 2H), 2.78 (brs, 1H), 2.97 (brs, 1H), 4.09 (m, 2H), 4.39 (t, 2H), 4.69 (m, 2H), 6.84 (s, 2H), 7.08 (s, 1H).

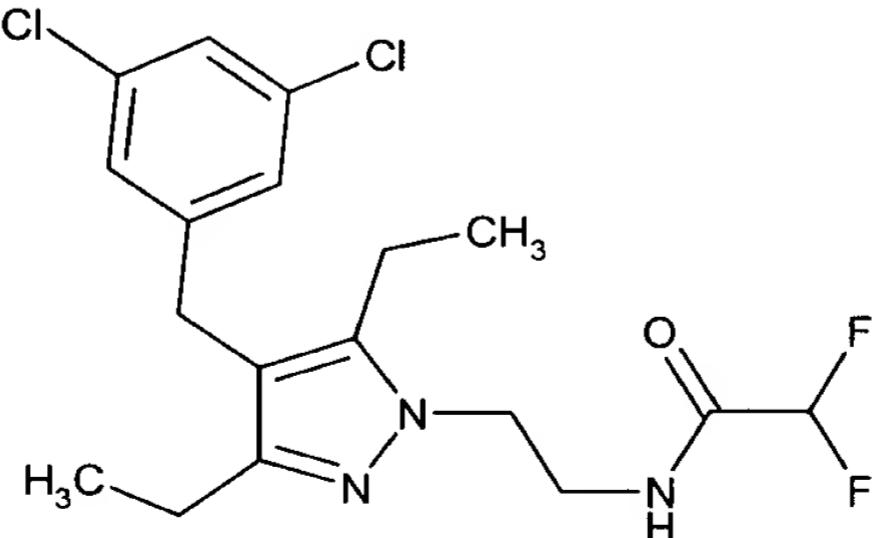
LRMS (electrospray): m/z [MNa⁺] 369.

20

Accurate Mass: Found 347.0394 [MH⁺]; C₁₄H₁₆Cl₂N₂O₂S requires 347.0383 [MH⁺].

Example 52

N-{2-[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-2,2-difluoroacetamide



Standard solution: The amine of Example 43 (372mg, 1.14mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (437mg, 2.28mmol) and 4-dimethylaminopyridine (342mg, 2.28mmol) were dissolved in dimethylformamide (14.25ml).

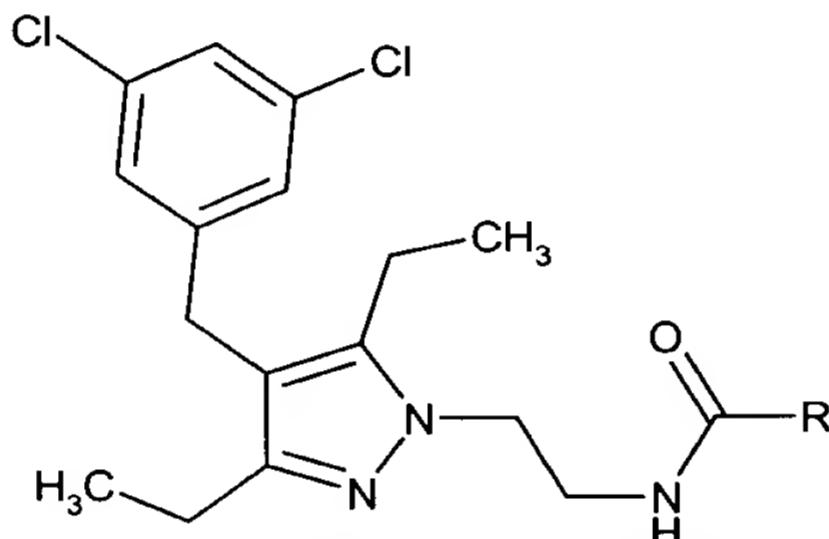
Difluoroacetic acid (2.5 μ l, 40 μ mol) was treated with the standard solution of amine 5 (250 μ L) in a 96 well plate and the mixture was shaken for 18 hours. The reaction mixture was filtered and the filtrate was purified by HPLC (Magellen C₈(2) 150x10mm column; a gradient mobile phase was used, 5:95 (by volume) \rightarrow 95:5 (by volume) acetonitrile: (water, 95% by volume/trifluoroacetic acid, 0.1% by volume/acetonitrile 5%, by volume)).

Retention time: 6.05 minutes

10 LRMS (electrospray): m/z [MH⁺] 404.

EXAMPLES 53-70

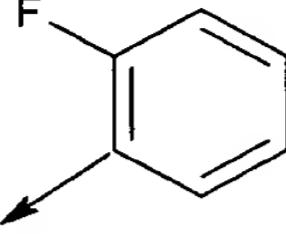
The compounds of the following tabulated Examples of the general formula:



were prepared by a similar method to that of Example 52 using the appropriate acid.

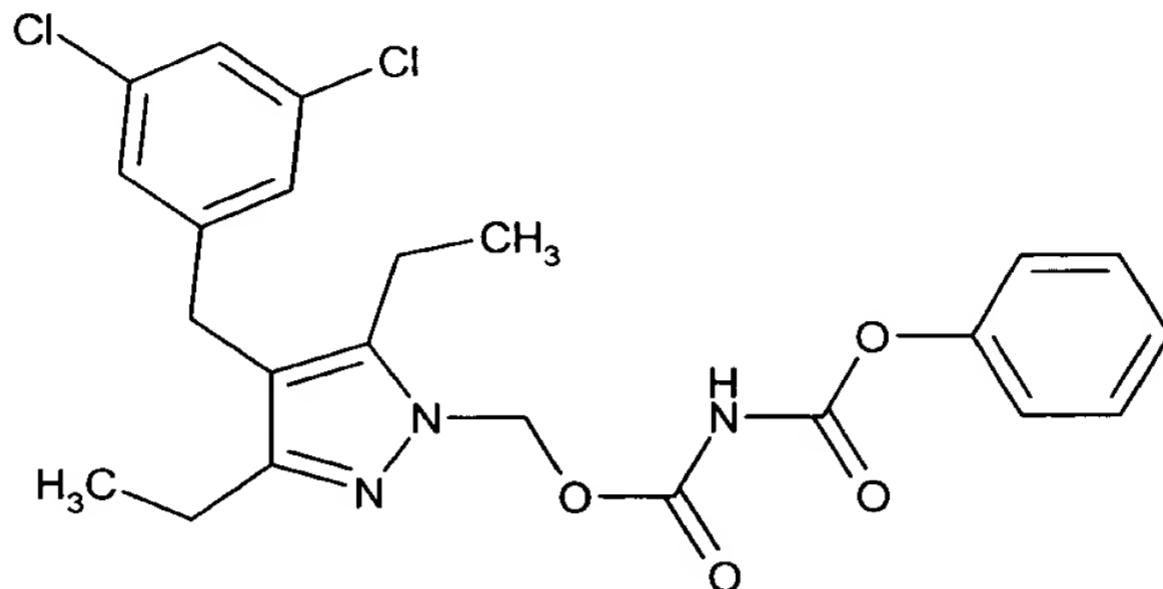
Example No.	R	HPLC retention time (minutes)	LRMS (electrospray) m/z [M ⁺] =
53		5.15	397
54		4.96	448
55		5.73	448
56		4.37	426

57		6.00	412
58		6.20	431
59		5.61	398
60		5.12	447
61		5.84	432
62		5.96	448
63		5.22	436
64		5.82	424
65		5.49	446
66		4.96	384
67		6.05	438
68		3.85	411
69		5.54	393

70		6.46	448
----	---	------	-----

Example 71

[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]methyl phenyl imidodicarbonate



5 A solution of the alcohol of Example 41 (6.3mg, 20μmol) in dimethylformamide (250μL) was treated with phenyl isocyanatoformate (3.6mg, 22μmol) and the mixture was shaken for 1.5 hours. The reaction mixture was filtered and the filtrate was purified by HPLC (Hypersil Thermoquest Luna C₈ 150x10mm column; a gradient mobile phase was used, 10:90 (by volume)→95:5 (by volume) acetonitrile:(water, 95% by volume/trifluoroacetic acid, 0.1% by volume/acetonitrile 5%, by volume)).

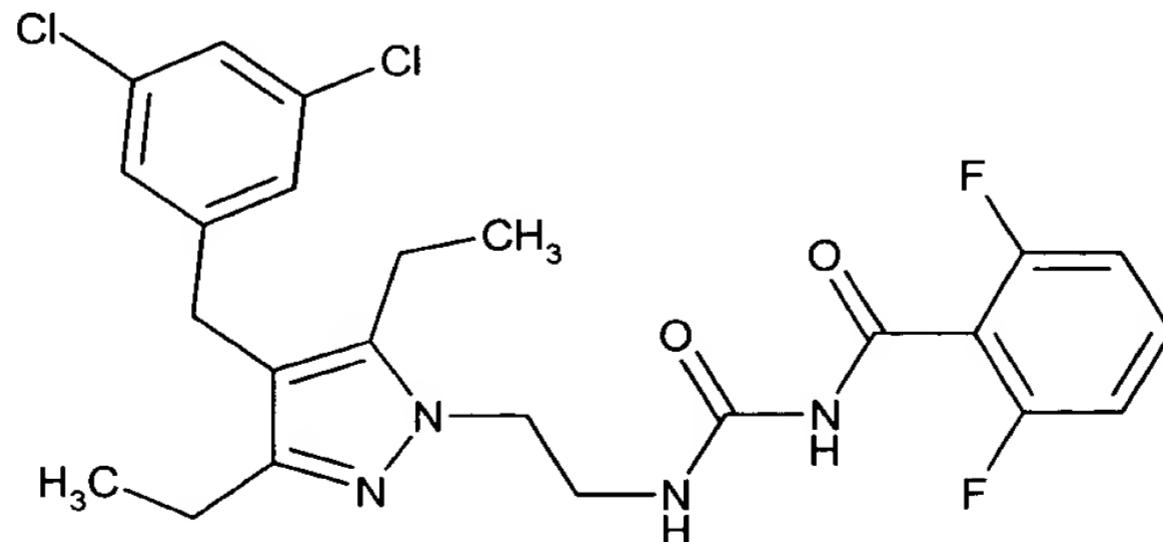
10

Retention time: 7.64 minutes

LRMS (electrospray): m/z [MH⁺] 476.

Example 72

N-[2-[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl]-N-(2,6-difluorobenzoyl)urea



15

A solution of the amine of Example 43 (6.5mg, 20μmol) in dimethylformamide (250μL) was treated with 2,6-difluorobenzoylisocyanate (4.0mg, 22μmol) and the mixture was shaken for 18 hours. The reaction mixture was filtered and the filtrate was purified by HPLC (Hypersil Thermoquest Luna C₈ 150x10mm column; a gradient mobile phase was used, 10:90

(by volume)→95:5 (by volume) acetonitrile:(water, 95% by volume/trifluoroacetic acid, 0.1% by volume/acetonitrile 5%, by volume)).

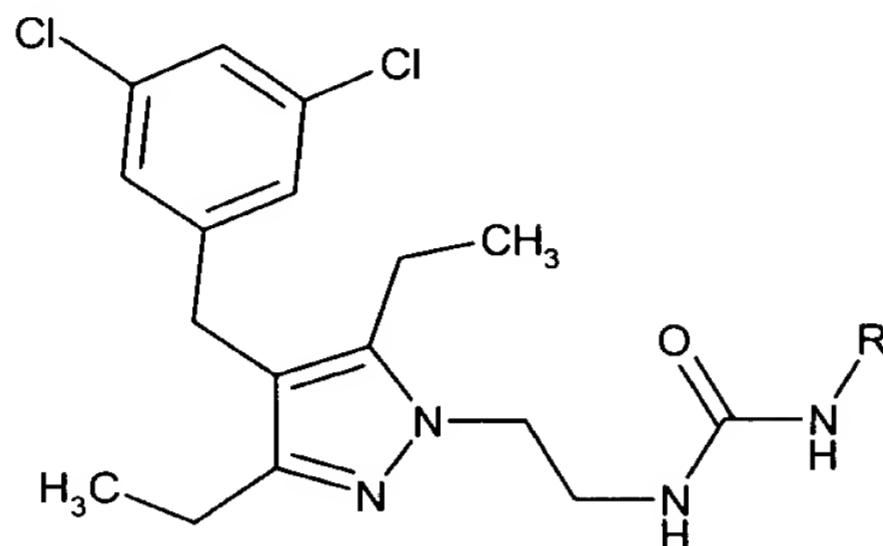
Retention time: 6.8-7.4 minutes

LRMS (electrospray): m/z [MH⁺] 509.

5

EXAMPLES 73-74

The compounds of the following tabulated Examples of the general formula:



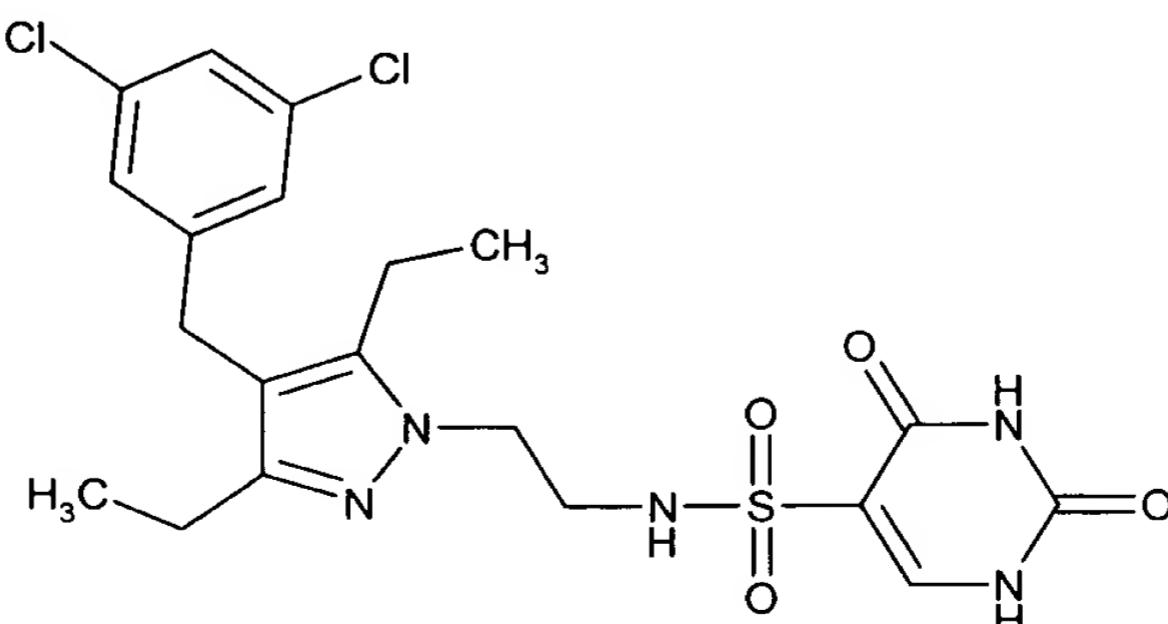
were prepared by a similar method to that of Example 72 using the appropriate isocyanate.

Example No.	R	HPLC retention time (minutes)	LRMS (electrospray) m/z [M ⁺]
73		6.23	411
74		7.21	473

10

Example 75

N-{2-[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1H-pyrazol-1-yl]ethyl}-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinesulfonamide



A solution of the amine of Example 43 (6.5mg, 20 μ mol) and triethylamine (6 μ L, 40 μ mol) in dimethylformamide (250 μ L) was treated with 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinesulfonyl chloride (J. Am. Chem. Soc., 1956, 78, 401) (0.8mg, 4.0 μ mol) and the mixture was shaken for 18 hours. The reaction mixture was filtered and the filtrate was
5 purified by HPLC (Hypersil Thermoquest Luna C₈ 150x10mm column; a gradient mobile phase was used, 10:90 (by volume) \rightarrow 95:5 (by volume) acetonitrile:(water, 95% by volume/trifluoroacetic acid, 0.1% by volume/acetonitrile 5%, by volume)).

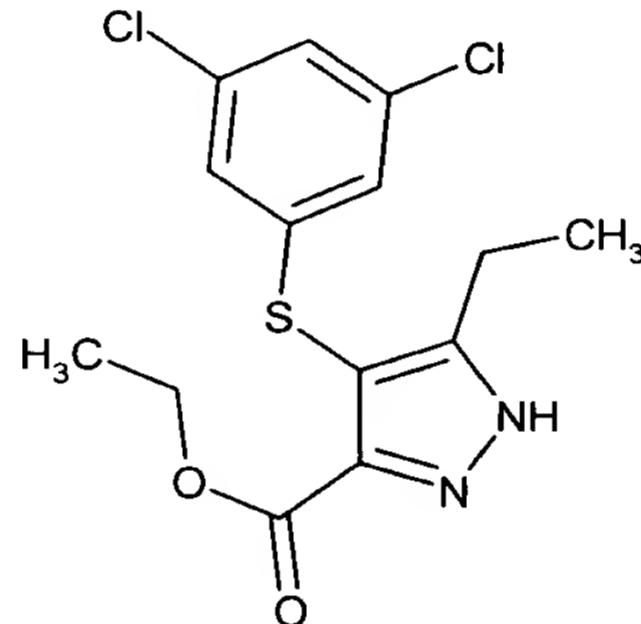
Retention time: 6.00 minutes

LRMS (electrospray): m/z [MH⁺] 500.

10

Example 76

Ethyl 4-[(3,5-dichlorophenyl)sulfanyl]-5-ethyl-1*H*-pyrazole-3-carboxylate



To a stirred solution of the β -diketone of Preparation 36 (2.00g, 5.73mmol) in ethanol
15 (3ml) was added hydrazine monohydrate (278 μ L, 5.73mmol) and the resulting mixture was heated at 80°C in a sealed Reacti-vial (Trade Mark) for 2 hours. After cooling, the mixture was dissolved in water and the resulting solution was extracted with dichloromethane and followed by ethyl acetate. The combined organic phases were washed with brine and concentrated under reduced pressure. The residue was purified by flash chromatography on
20 silica gel eluting with cyclohexane:ethyl acetate (5:1, by volume) and then cyclohexane:ethyl acetate (3:1, by volume) to afford the product as an oily white solid. This material was washed with pentane and the white solid was collected by filtration and air dried to give a pure sample of the title compound (450mg), m.p. 138-139°C.

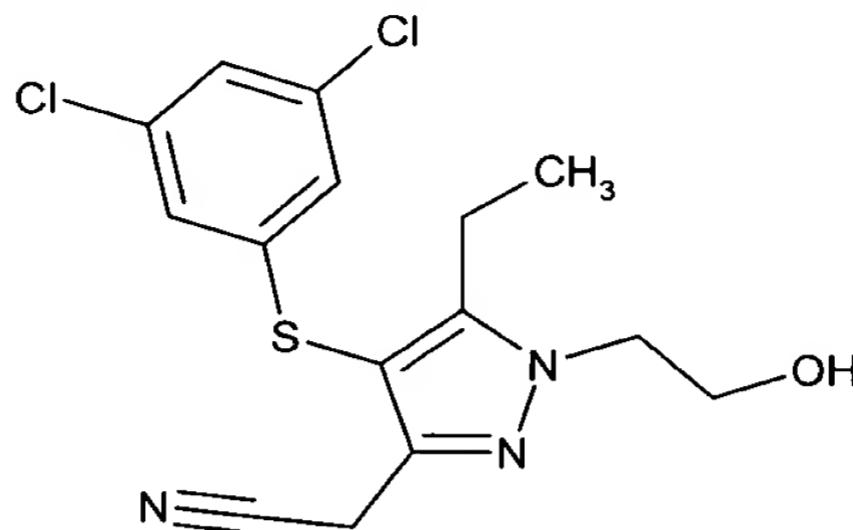
¹H-NMR (400MHz, CDCl₃): δ = 1.21 (m, 6H), 2.72 (q, 2H), 4.32 (q, 2H), 6.84 (s, 2H),
25 7.04 (s, 1H).

LRMS (electrospray): m/z [M-H⁺] 343.

Microanalysis: Found: C, 48.53; H, 3.95; N, 8.00. C₁₄H₁₄Cl₂N₂O₂S requires C, 48.71; H, 4.09; N, 8.11%.

Example 77

[4-[(3,5-Dichlorophenyl)sulfanyl]-5-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-3-yl]acetonitrile



A solution of the protected alcohol of Preparation 39 (70mg, 0.15mmol) in
5 tetrahydrofuran (1ml) was treated with tetrabutylammonium fluoride (1M in THF) (300 μ L, 0.30mmol), at room temperature. After the reaction mixture had stirred for 3 hours the solution was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (3:1, by volume) to afford the title compound (30mg) as a white solid, m.p. 84-85°C.

10 $^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 1.15 (m, 3H), 2.75 (q, 2H), 2.83 (t, 1H), 3.63 (s, 2H), 4.12 (m, 2H), 4.22 (m, 2H), 6.82 (s, 2H), 7.10 (s, 1H).

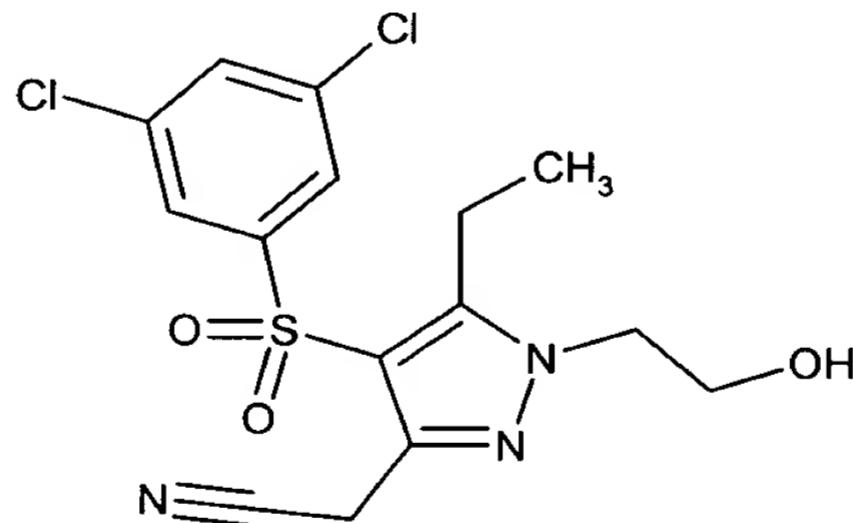
LRMS (electrospray): m/z [M-H $^+$] 354.

Microanalysis: Found: C, 50.86; H, 4.28; N, 11.70. $\text{C}_{15}\text{H}_{15}\text{Cl}_2\text{N}_3\text{OS}$ requires C, 50.57; H, 4.24; N, 11.79%.

15

Example 78

[4-[(3,5-Dichlorophenyl)sulfonyl]-5-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-3-yl]acetonitrile



To a stirred solution of the pyrazole (68mg, 0.14mmol) of Preparation 39 in methanol (2ml) was added dichloromethane (3ml), followed by meta-chloroperoxybenzoic acid (60% w/w) (125mg, 0.43mmol). After 18 hours the mixture was partitioned between dichloromethane and water. The aqueous component was separated and further extracted with dichloromethane. The combined organic phases were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give a white solid. To a stirred solution of this material in THF (2ml) was added water (2ml) followed by acetic acid (2ml).
25 After 18 hours at room temperature the mixture was partitioned between water and

dichloromethane and the aqueous component was separated and further extracted with dichloromethane. The combined organic phases were washed with aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (2:1, by volume) followed by cyclohexane:ethyl acetate (1:1, by volume) to afford the title compound (45mg) as a white solid, m.p. 117-118°C.

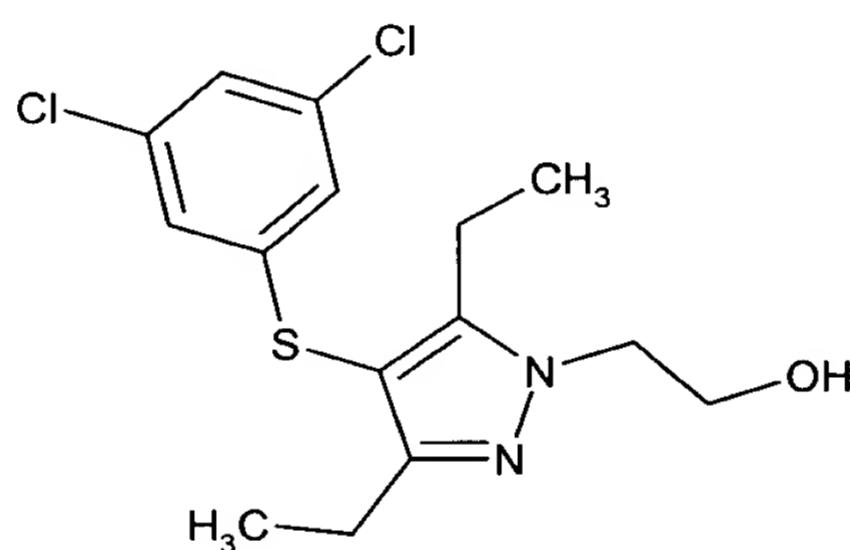
5 ¹H-NMR (400MHz, CDCl₃): δ = 1.11 (t, 3H), 2.41 (t, 1H), 2.89 (q, 2H), 4.02 (s, 2H), 4.05 (m, 4H), 7.57 (s, 2H), 7.79 (s, 1H).

10 LRMS (electrospray): m/z [MH⁺] 388.

Microanalysis: Found: C, 46.39; H, 3.89; N, 10.53. C₁₅H₁₅Cl₂N₃O₃S requires C, 46.40; H, 3.89; N, 10.82%.

Example 79

2-{4-[(3,5-Dichlorophenyl)sulfanyl]-3,5-diethyl-1*H*-pyrazol-1-yl}ethanol



15 To a stirred solution of the diketone (500mg, 1.64mmol) of Preparation 41 in ethanol (1ml) was added 2-hydroxyethylhydrazine (113μl, 1.80mmol). The reaction mixture was heated at 80°C in a sealed Reacti-vial (Trade Mark) for 4 hours. After cooling, the mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with pentane:ethyl acetate (3:1, by volume) to afford the title compound as a yellow solid (349mg), 77-79°C.

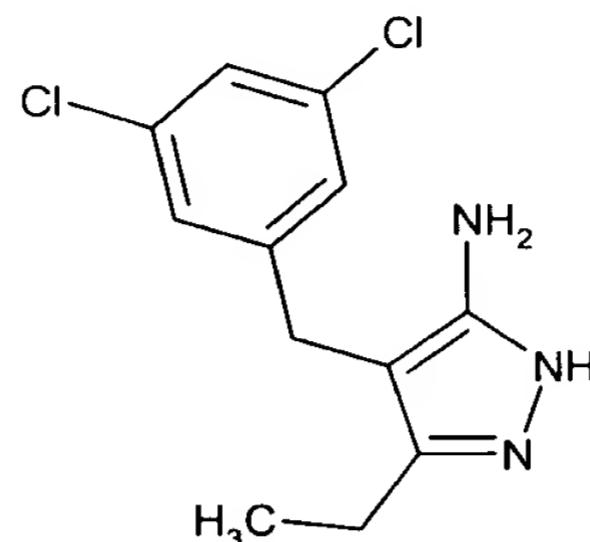
20 ¹H-NMR (400MHz, CDCl₃): δ = 1.04 (t, 3H), 1.18 (t, 3H), 2.52 (q, 2H), 2.62 (q, 2H), 3.64 (s, 1H), 4.03 (m, 2H), 4.17 (m, 2H), 6.79 (s, 2H), 7.02 (s, 1H).

25 LRMS (electrospray): m/z [MH⁺] 345.

Microanalysis: Found: C, 51.88; H, 5.20; N, 8.03. C₁₅H₁₈Cl₂N₂OS requires C, 52.18; H, 5.25; N, 8.11%.

Example 80

4-(3,5-Dichlorobenzyl)-3-ethyl-1*H*-pyrazol-5-amine



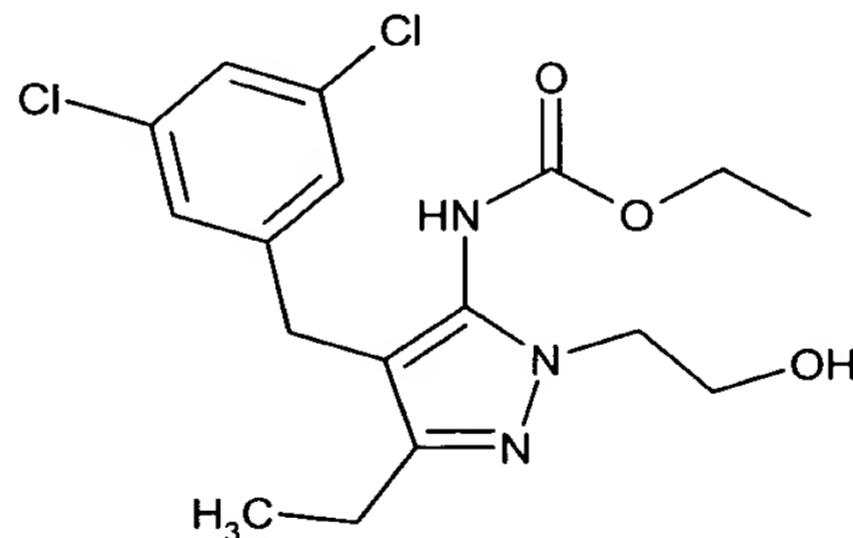
To a stirred solution of the nitrile (500mg, 1.95mmol) of Preparation 43 in ethanol 5 (50ml) was added hydrazine monohydrate (100mg, 1.95mmol) and the mixture was heated under reflux. After 15 hours the reaction mixture was cooled and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:5:0.5, by volume) to afford the title compound as a yellow oil (250mg).

10 ¹H-NMR (400MHz, CD₃OD): δ = 1.05 (t, 3H), 2.43 (q, 2H), 3.66 (s, 2H), 7.09 (s, 2H), 7.19 (s, 1H).

LRMS (thermospray): m/z [MH⁺] 345.

Example 81

Ethyl 4-(3,5-dichlorobenzyl)-3-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-5-ylcarbamate



15 To a stirred solution of the pyrazole (150mg, 0.35mmol) of Preparation 44 and triethylamine (70μl, 0.53mmol) in dichloromethane (6ml) was added ethyl chloroformate (40μl, 0.39mmol) and the mixture was heated under reflux. After 15 hours the solution was concentrated under reduced pressure. To a solution of the residue in pyridine (2ml) was added ethyl chloroformate (40μl, 0.39mmol). After 7 days at room temperature the solvent 20 was removed under reduced pressure and the residue was filtered through silica, eluting with dichloromethane:methanol:ammonia (98:2:0.2, by volume). The resulting solution was concentrated under reduced pressure and the residue was dissolved in a mixture of tetrahydrofuran (2ml), acetic acid (2ml) and water (1ml). After stirring at room temperature for 25 15 hours the reaction mixture was partitioned between water and dichloromethane. The

aqueous phase was separated and further extracted with dichloromethane. The combined organic phases were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane followed by 5 dichloromethane:methanol:ammonia (95:5:0.5, by volume) to afford the title compound (18mg) as a colourless oil.

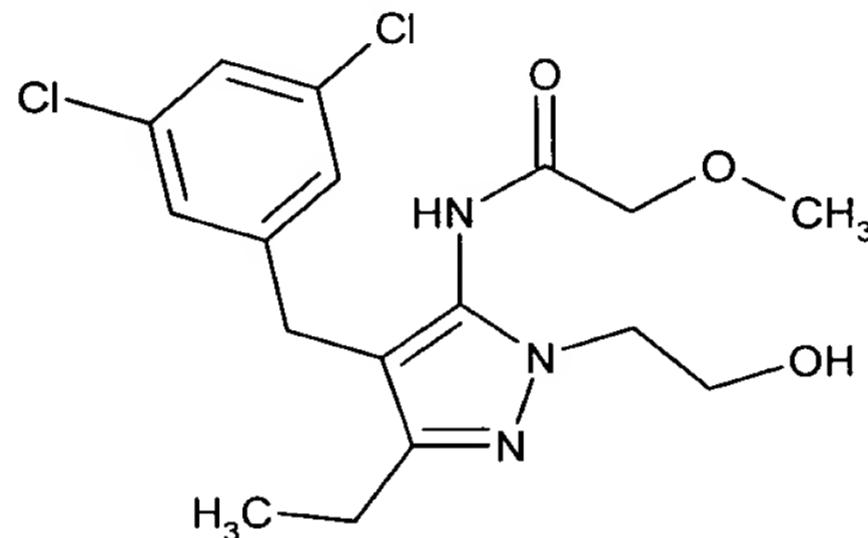
¹H-NMR (300MHz, CDCl₃): δ = 1.20 (m, 6H), 2.49 (m, 2H), 3.71 (s, 2H), 3.99 (m, 2H), 4.10 (m, 4H), 6.30 (m, 1H), 7.03 (s, 2H), 7.20 (s, 1H).

LRMS (electrospray): m/z [M-H⁺] 384.

10

Example 82

N-[4-(3,5-Dichlorobenzyl)-3-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-5-yl]-2-methoxyacetamide



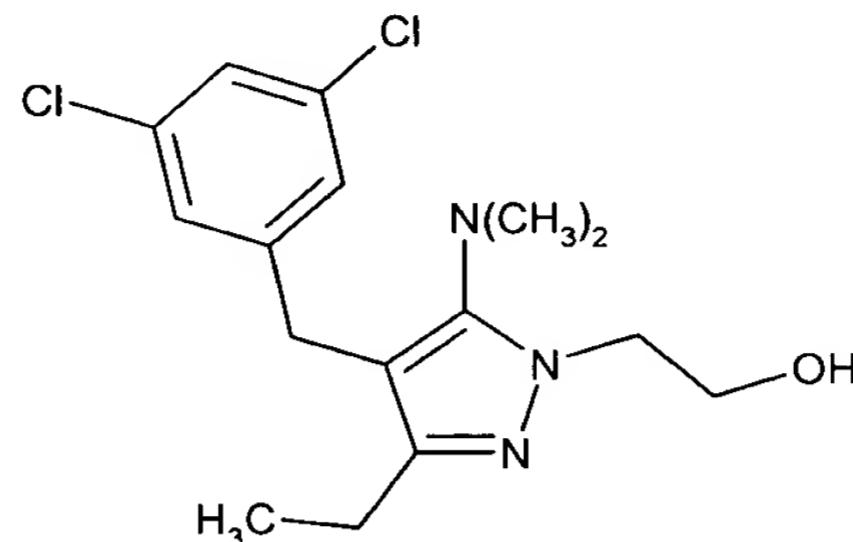
To a stirred mixture of the pyrazole (200mg, 0.47mmol) of Preparation 44 and methoxyacetyl chloride (56mg, 0.52mmol) in dichloromethane (10ml) was added triethylamine (72μl, 0.52mmol). After 15 hours at room temperature the solvent was removed under reduced pressure and the resulting orange oil was partitioned between dichloromethane and water. The organic phase was separated, washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. To a stirred solution of the residue in acetic acid (2ml) was added water (1ml). After 3 days at room temperature 15 the mixture was heated at 60°C. After 4 hours the solution was cooled to room temperature and partitioned between aqueous sodium carbonate solution and dichloromethane. The organic phase was separated and twice washed with water, twice washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The 20 title compound was isolated as a white solid (100mg) which was used without further purification, m.p. 142-144°C.

¹H-NMR (400MHz, CF₃CO₂D): δ = 1.38 (t, 3H), 2.90 (q, 2H), 3.52 (s, 3H), 3.88 (s, 2H), 4.16 (s, 2H), 4.21 (m, 2H), 4.58 (m, 2H), 7.03 (s, 2H), 7.30 (s, 1H).

LRMS (thermospray): m/z [MH⁺] 386.

Example 83

2-[4-(3,5-Dichlorobenzyl)-5-(dimethylamino)-3-ethyl-1*H*-pyrazol-1-yl]ethanol



A stirred solution of the pyrazole (300mg, 0.70mmol) of Preparation 44 and paraformaldehyde (46mg, 1.54mmol) in formic acid (2ml) was heated under reflux. After 15 hours the mixture was cooled and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane followed by dichloromethane:methanol (99:1, by volume) to afford the title compound (50mg) as a colourless oil.

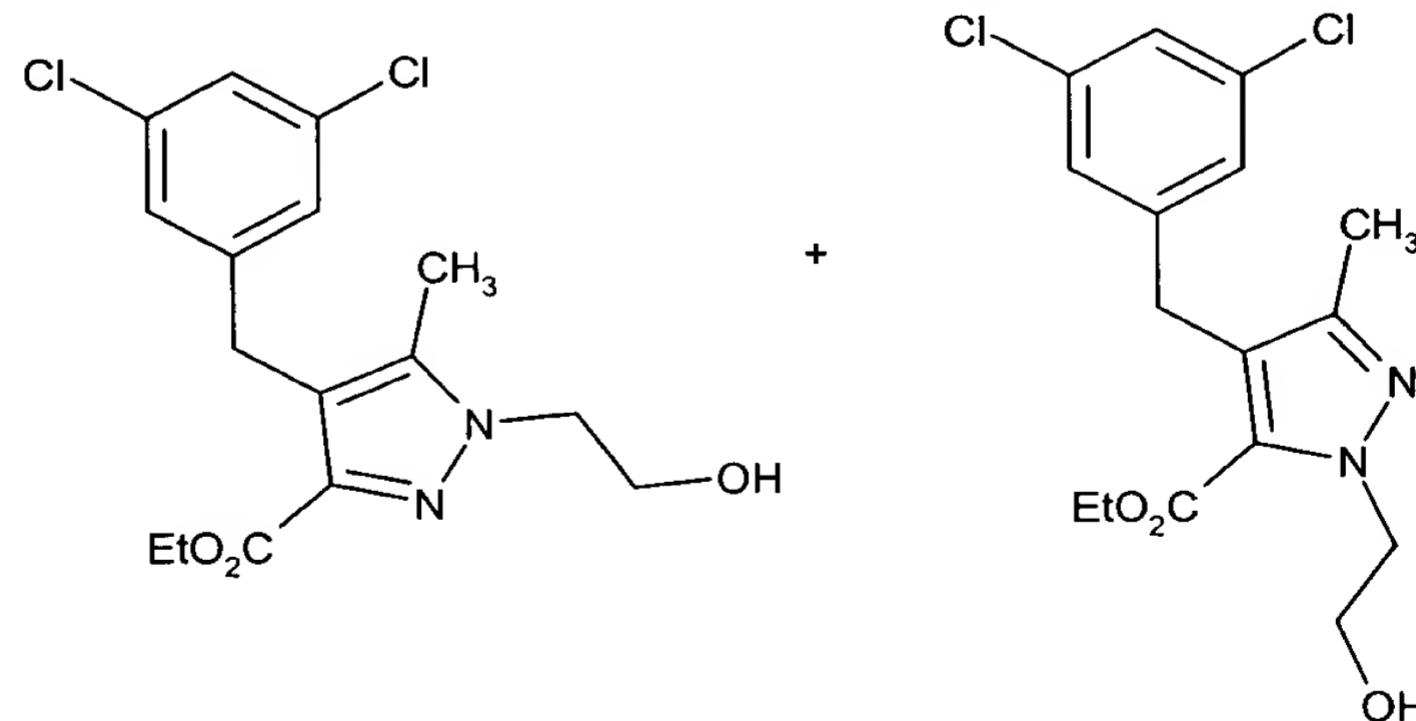
¹⁰ ¹H-NMR (400MHz, CDCl₃): δ = 1.09 (t, 3H), 2.38 (q, 2H), 2.62 (s, 6H), 3.77 (s, 2H), 3.91 (m, 2H), 4.04 (m, 2H), 4.23 (t, 1H), 6.95 (s, 2H), 7.17 (s, 1H).

LRMS (thermospray): m/z [MH⁺] 342.

EXAMPLES 84 and 85

Ethyl 4-(3,5-dichlorobenzyl)-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazole-3-carboxylate

¹⁵ (Examples 84) and ethyl 4-(3,5-dichlorobenzyl)-1-(2-hydroxyethyl)-3-methyl-1*H*-pyrazole-5-carboxylate (Example 85)



The title compounds were prepared by a similar method to that of Examples 27 and 28 using the β-diketone of Preparation 22. The crude product was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (1:1, by volume) to afford the two isomers.

Less polar isomer (Example 85):

Shown to be ethyl 4-(3,5-dichlorobenzyl)-1-(2-hydroxyethyl)-3-methyl-1*H*-pyrazole-5-carboxylate by nOe experiments. Isolated as a white solid, m.p. 105.8-107.5°C.

5 $^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 1.35 (t, 3H), 2.20 (s, 3H), 3.10 (t, 1H), 4.00 (s, 2H),
4.01 (m, 2H), 4.30 (q, 2H), 4.67 (m, 2H), 6.98 (s, 2H), 7.20 (s, 1H).

LRMS (thermospray): m/z [MH $^+$] 357.

Microanalysis: Found: C, 53.81; H, 5.02; N, 7.59. $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_3$ requires C, 53.80; H,
5.08; N, 7.84%.

More polar isomer (Example 84):

10 Ethyl 4-(3,5-dichlorobenzyl)-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazole-3-carboxylate
was isolated as a white solid, 110.7-112.4°C.

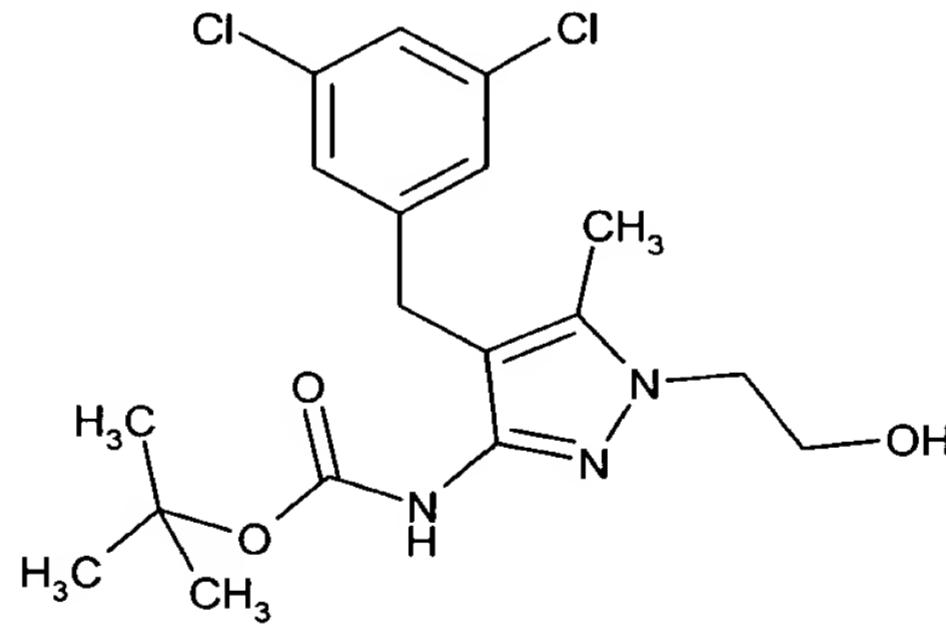
15 $^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 1.35 (t, 3H), 2.21 (s, 3H), 2.70 (brs, 1H), 4.01 (m, 4H),
4.22 (m, 2H), 4.33 (q, 2H), 7.00 (s, 2H), 7.19 (s, 1H).

LRMS (thermospray): m/z [MH $^+$] 357.

15 Microanalysis: Found: C, 53.53; H, 5.06; N, 7.59. $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_3$ requires C, 53.80; H,
5.08; N, 7.84%.

Example 86

tert-Butyl 4-(3,5-dichlorobenzyl)-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-3-ylcarbamate



20 A suspension of the carboxylic acid of Preparation 23 (550mg, 1.67mmol) in *tert*-butanol (8.35ml) was treated with triethylamine (244 μL , 1.84mmol) and diphenylphosphoryl azide (396 μL , 1.84mmol) and the reaction mixture was stirred under reflux for 18 hours, under a nitrogen atmosphere. After cooling, the solution was concentrated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (x3). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (1:2, by volume) followed by dichloromethane:methanol:ammonia (95:5:0.5, by volume) to afford the title compound (160mg).

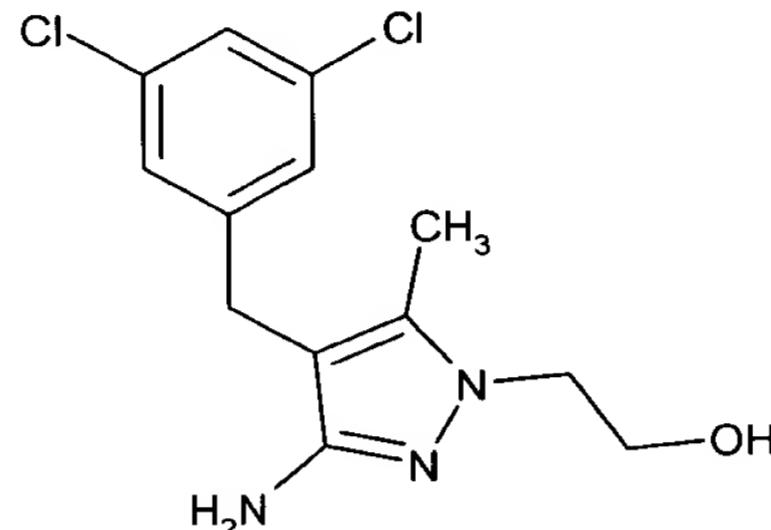
¹H-NMR (300MHz, CDCl₃): δ = 1.44 (s, 9H), 2.17 (s, 3H), 3.42 (s, 1H), 3.77 (s, 2H), 3.92 (m, 2H), 4.02 (m, 2H), 6.43 (s, 1H), 6.99 (s, 2H), 7.18 (s, 1H).

LRMS (thermospray): m/z [MH⁺] 400.

EXAMPLE 87

5

2-[3-Amino-4-(3,5-dichlorobenzyl)-5-methyl-1*H*-pyrazol-1-yl]ethanol



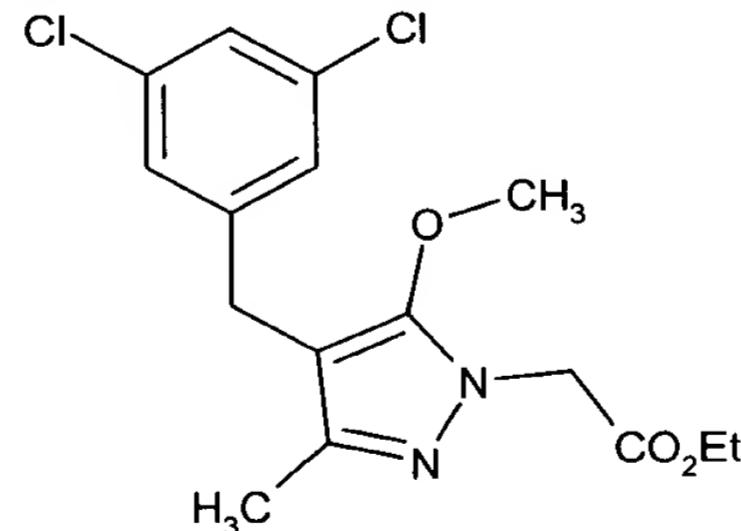
A solution of the protected amine of Example 86 (50mg, 0.13mmol) in 1,4-dioxan was treated with 4M hydrogen chloride in 1,4-dioxan (320μL, 1.25mmol) and stirred at room temperature for 2 days. The solution was concentrated under reduced pressure. The residue 10 was diluted with water (15ml) and extracted with ethyl acetate (3x10ml). The combined organic phases were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to afford the title compound as a white solid and as the hydrochloride salt (19.5mg).

¹H-NMR (300MHz, d₆-DMSO): δ = 2.13 (s, 3H), 3.59 (m, 2H), 3.69 (s, 2H), 3.89 (m, 2H), 7.09 (s, 2H), 7.25 (s, 1H).

LRMS (thermospray): m/z [MH⁺] 300.

Example 88

Ethyl [4-(3,5-dichlorobenzyl)-5-methoxy-3-methyl-1*H*-pyrazol-1-yl]acetate



20 A suspension of the ester of Preparation 26 (100mg, 0.29mmol) in toluene (4ml) was treated with triphenylphosphine (115mg, 0.44mmol), followed by methanol (15μL, 0.30mmol) then diethyl azodicarboxylate (69μL, 0.44mmol) and the resulting mixture was stirred at room temperature, under a nitrogen atmosphere for 18 hours. The reaction mixture was diluted with ethyl acetate and washed with 10% aqueous sodium carbonate solution. The organic phase 25 was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced

pressure. The resulting oil was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (3:1, by volume) to afford the title compound (73mg) as a colourless oil, which solidified under reduced pressure.

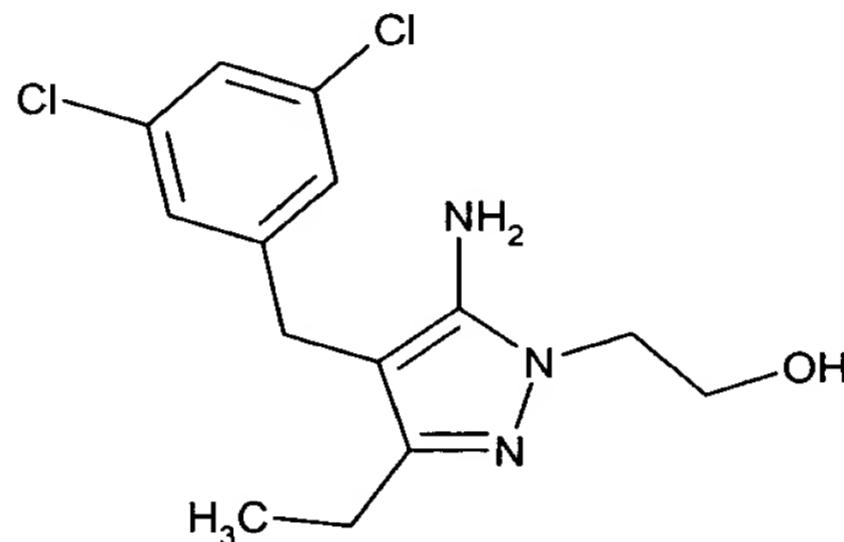
5 $^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 1.31 (t, 3H), 2.08 (s, 3H), 3.78 (s, 2H), 3.81 (s, 3H),
4.27 (q, 2H), 4.73 (s, 2H), 7.03 (s, 2H), 7.20 (s, 1H).

LRMS (thermospray): m/z [MH $^+$] 357.

Microanalysis: Found: C, 53.66 H, 5.08; N, 7.84. $\text{C}_{16}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_3$ requires C, 53.80; H,
5.08; N, 7.84%.

Example 89

10 2-[5-Amino-4-(3,5-dichlorobenzyl)-3-ethyl-1*H*-pyrazol-1-yl]ethanol



To a stirred solution of the nitrile (500mg, 1.95mmol) of Preparation 43 in ethanol (50ml) was added 2-hydroxyethylhydrazine (153mg, 1.95mmol) and the mixture was heated under reflux. After 15 hours the mixture was concentrated under reduced pressure. The 15 crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:5:0.5, by volume) to afford the title compound (450mg) as a white solid, m.p. 135°C.

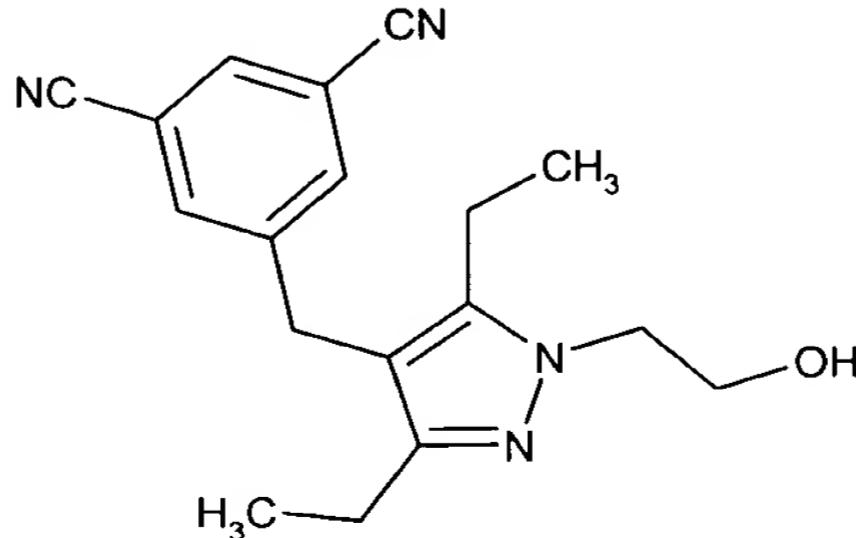
18 $^1\text{H-NMR}$ (400MHz, DMSO): δ = 0.90 (t, 3H), 2.19 (q, 2H), 3.58 (m, 4H), 3.82 (t, 2H),
4.82 (t, 1H), 4.90 (s, 2H), 7.07 (s, 2H), 7.30 (s, 1H).

20 LRMS (thermospray): m/z [MH $^+$] 314.

Microanalysis: Found: C, 53.33; H, 5.50; N, 13.20. $\text{C}_{14}\text{H}_{17}\text{Cl}_2\text{N}_3\text{O}$ requires C, 53.52;
H, 5.45; N, 13.37%.

Example 90

5-{[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]methyl}isophthalonitrile



2-Hydroxyethylhydrazine (34mg, 0.44mmol) was added to a stirred solution of the diketone (105mg, 0.4mmol) of Preparation 45 in glacial acetic acid (3ml) at room temperature under nitrogen. After stirring for 3 days the acetic acid was evaporated under reduced pressure and the residue was partitioned between 10% aqueous potassium carbonate solution (40ml) and dichloromethane (40ml). The organic phase was separated, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (98:2, by volume) to give the title compound as a white solid (76mg) m.p. 115-117°C.

10 ¹H-NMR (400MHz, CDCl₃): δ = 1.0 (3H, t), 1.1 (3H, t), 1.55 (1H, br.s), 2.37 (2H, q), 2.48 (2H, q), 3.79 (2H, s), 4.02 (2H, m), 4.08 (2H, m), 7.55 (2H, s), 7.71 (1H, s).

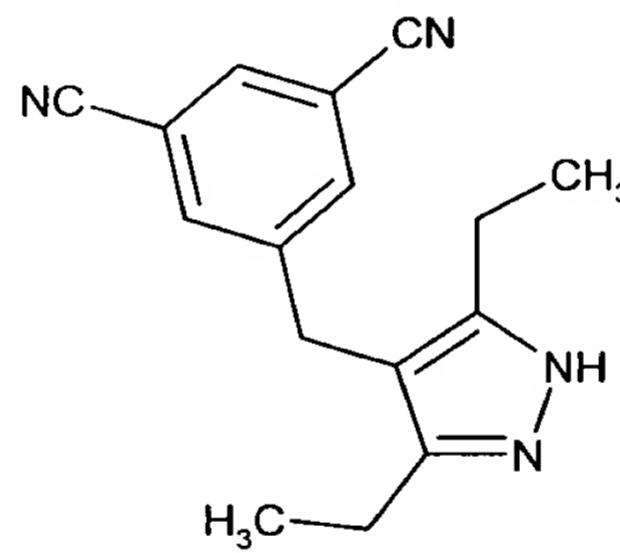
LRMS (thermospray): m/z [MH⁺] 309.

Microanalysis: Found: C, 69.64; H, 6.54; N, 18.06. C₁₆H₁₆N₂O₂ requires C, 70.11; H, 6.54; N, 18.17%.

15

Example 91

5-[(3,5-Diethyl-1*H*-pyrazol-4-yl)methyl]isophthalonitrile



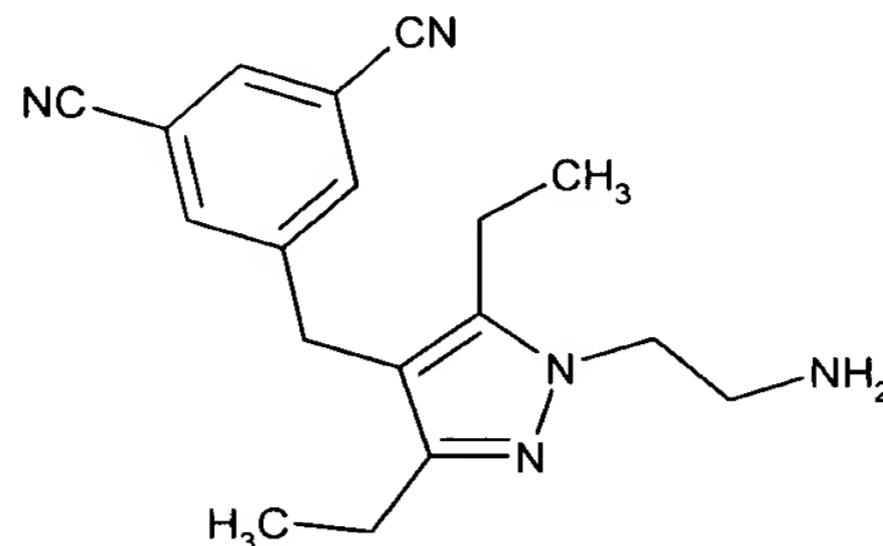
Hydrazine hydrate (49μL, 1mmol) was added to a stirred solution of the diketone (237mg, 0.9mmol) of Preparation 45 in glacial acetic acid (3ml) at room temperature under nitrogen. After stirring for 3 days the acetic acid was evaporated under reduced pressure and the residue was partitioned between 10% aqueous potassium carbonate solution (40ml) and dichloromethane (40ml). The organic phase was separated, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (98:2, by volume) to give the title compound as a white solid (188mg) m.p. 141-143°C.

1H-NMR (400MHz, CDCl₃): δ = 1.15 (6H, t), 2.47 (4H, q), 3.82 (2H, s), 7.58 (2H, s), 7.73 (1H, s).

LRMS (thermospray): m/z [MH⁺] 265.

Example 92

5-{{[1-(2-Aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]methyl}isophthalonitrile}



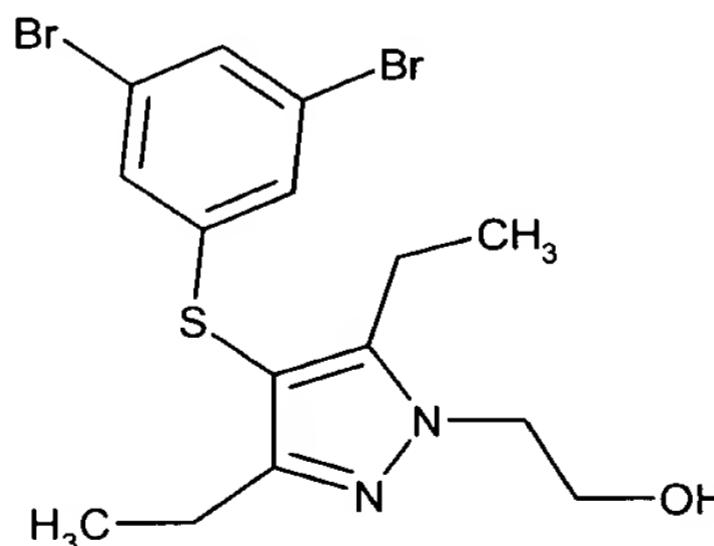
A stirred mixture of the pyrazole (106mg, 0.4mmol) of Example 91 and 2-chloroethylamine hydrochloride (70mg, 0.6mmol) was heated at 150°C under nitrogen for 18 hours. After cooling the mixture was partitioned between 10% aqueous potassium carbonate (40ml) and dichloromethane (40ml) and the organic layer was dried over magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol (98:2, by volume) and then dichloromethane:methanol:0.880 ammonia (95:5:0.5, by volume) to give the title compound as a white solid (51mg) m.p. 100-105°C.

¹H-NMR (400MHz, CDCl₃): δ = 1.02 (3H, t), 1.09 (3H, t), 1.49 (2H, br.s), 2.38 (2H, q), 2.52 (2H, q), 3.13 (2H, t), 3.78 (2H, s), 4.04 (2H, t), 7.58 (2H, s), 7.74 (1H, s).

LRMS (electrospray): m/z [MH⁺] 308.

Example 93

2-{4-[(3,5-Dibromophenyl)sulfanyl]-3,5-diethyl-1*H*-pyrazol-1-yl}ethanol



2-Hydroxyethylhydrazine (0.43mL, 6.3mmol) was added to a suspension of the diketone (2.5g, 6.3mmol) from Preparation 49 in glacial acetic acid (2ml) and the mixture was stirred for three days. 2-Hydroxyethylhydrazine (0.5mL, 7.3mmol) was added and the mixture was stirred for 16 hours. The mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate (100ml) and water (150ml). The aqueous layer was extracted with ethyl acetate (100ml) and the combined organic layers were washed with brine (100ml), dried over magnesium sulphate, filtered and concentrated under reduced

pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane gradually changing to dichloromethane:ethyl acetate (17:3, by volume) to provide the title compound (1.3g) as a colourless oil.

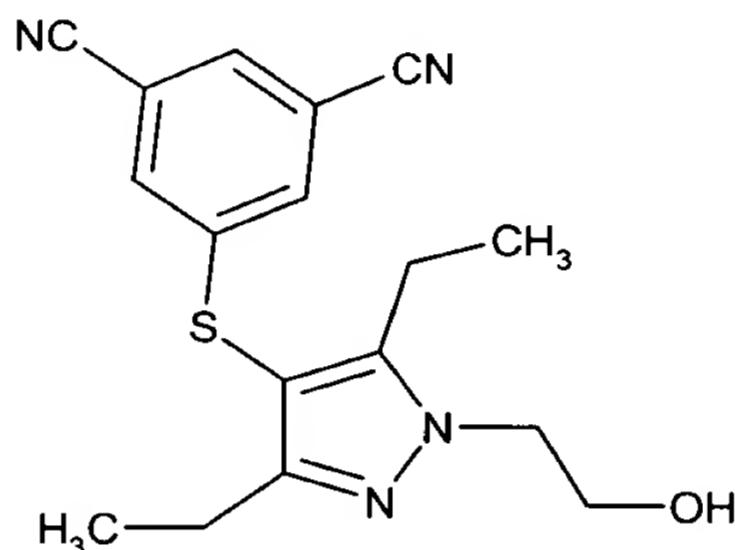
1 $^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 1.11 (t, 3H), 1.20 (t, 3H), 2.6 (q, 2H), 2.7 (q, 2H), 4.10
5 (m, 2H), 4.18 (m, 2H), 7.02 (s, 2H), 7.37 (s, 1H).

LRMS (thermospray): m/z [MH $^+$] 435.

Microanalysis: Found: C, 41.29; H, 4.17; N, 6.36. $\text{C}_{15}\text{H}_{18}\text{Br}_2\text{N}_2\text{OS}$ requires C, 41.49; H, 4.18; N, 6.45%.

Example 94

10 5-{{[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]sulfanyl}isophthalonitrile}



5-{{[1-(2-{{[tert-Butyl(dimethyl)silyl]oxy}ethyl}-3,5-diethyl-1*H*-pyrazol-4-yl]sulfanyl}isophthalonitrile (180mg, 0.4mmol) (Preparation 51) was treated with tetrabutylammonium fluoride (1M solution in tetrahydrofuran, 0.8ml, 0.8mmol) and the 15 resulting solution was stirred for $2\frac{1}{2}$ hours. The mixture was concentrated under reduced pressure to give a brown oil. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate:dichloromethane (1:4, by volume) to provide the title compound (70mg) as a yellow oil.

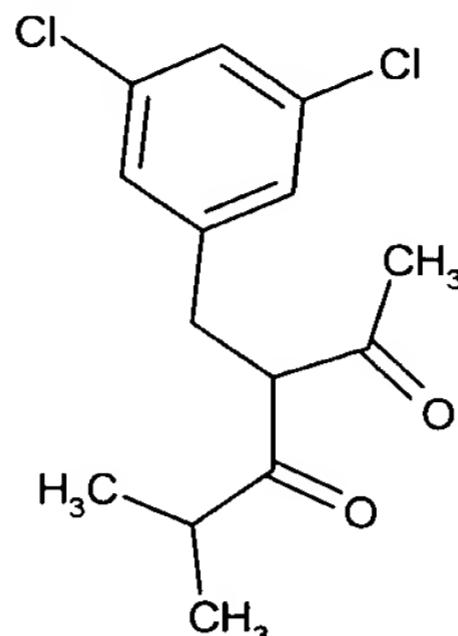
1 $^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 1.11 (t, 3H), 1.19 (t, 3H), 2.56 (q, 2H), 2.69 (q, 2H),
20 3.50 (br.s, 1H), 4.12 (m, 2H), 4.22 (m, 2H), 7.41 (s, 2H), 7.61 (s, 1H).

LRMS (electrospray): m/z [MH $^+$] 327.

The following Preparations describe the preparation of certain intermediates used in the preceding Examples.

PREPARATION 1

3-(3,5-Dichlorobenzyl)-5-methyl-2,4-hexanedione



5

Method A:

5% Palladium on barium sulphate (10mg) was added to a stirred solution of the more polar alkene isomer of Preparation 8 (100mg) in ethanol (2.5ml) and the resulting mixture was stirred under an atmosphere of hydrogen (103.4kPa, 15 psi) for 3 hours. The mixture was 10 filtered through a filter aid (Arbocel (Trade Mark))(caution - fire hazard) and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (10:1, by volume) to give the title compound (72mg) as a 43:57 mixture with its enol tautomer as estimated by ¹H-NMR and as a yellow oil.

¹H-NMR (400MHz, CDCl₃): δ = 1.03 (d, 6H, diketone and enol), 2.02 (s, 3H, enol), 15 2.11 (s, 3H, diketone), 2.52 (heptet, 1H, diketone), 2.61 (heptet, 1H, d, enol), 3.00 (dd, 1H, diketone), 3.06 (dd, 1H, diketone), 3.60 (s, 2H, enol), 4.00 (t, 1H, diketone), 6.98 and 7.00 (2s, 2x2H, diketone and enol), 7.18 (s, 1H, diketone and enol).

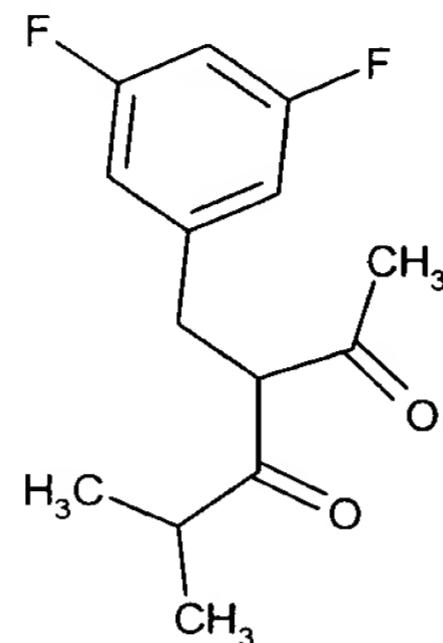
LRMS (thermospray): m/z [MH⁺] 304.

Method B:

20 The less polar alkene isomer of Preparation 8 was reduced in the same way as for the more polar isomer in Method A above but stirring the mixture for 9 hours and flash chromatography on silica gel eluting with a solvent gradient of pentane:ether (20:1, by volume) then pentane:ether (10:1, by volume) to give the title compound as a yellow oil.

PREPARATION 2

3-(3,5-Difluorobenzyl)-5-methyl-2,4-hexanedione



Method A:

5 5% Palladium on barium sulphate (56mg) was added to a stirred solution of the more polar alkene isomer of Preparation 11 (560mg) in ethanol (16ml) and the resulting mixture was stirred under an atmosphere of hydrogen (103.4kPa, 15 psi) for 4 hours. The mixture was filtered through a filter aid (Arbocel (Trade Mark))(caution - fire hazard) and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with pentane:ether (10:1, by volume) to give the title compound (513.1mg) as a 35:65 mixture with its enol tautomer as estimated by ¹H-NMR as a yellow oil.

10 ¹H-NMR (400MHz, CDCl₃): δ = 1.03 (d, 6H, diketone and enol), 2.03 (s, 3H, enol), 2.13 (s, 3H, diketone), 2.55 (heptet, 1H, diketone), 2.65 (heptet, 1H, enol), 3.03 (dd, 1H, diketone), 3.11 (dd, 1H, diketone), 3.65 (s, 2H, enol), 4.03 (t, 1H, diketone), 6.65 (m, 3H, diketone and enol).

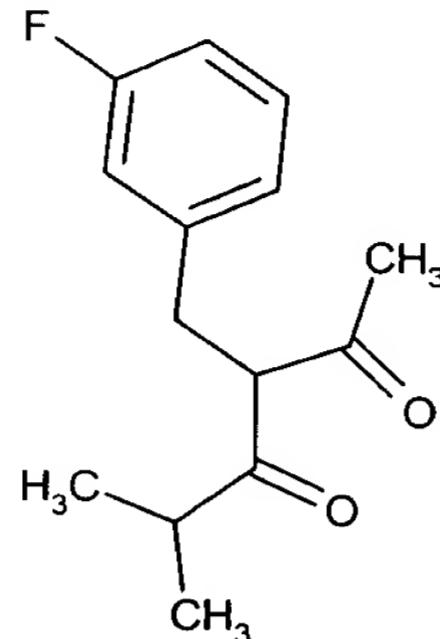
15 LRMS (electrospray): m/z [MNa⁺] 277.

Method B:

20 The less polar alkene isomer of Preparation 11 was reduced in the same way as for the more polar isomer in Method A above but stirring the mixture for 25 hours to give the title compound as a yellow oil.

PREPARATION 3

3-(3-Fluorobenzyl)-5-methyl-2,4-hexanedione



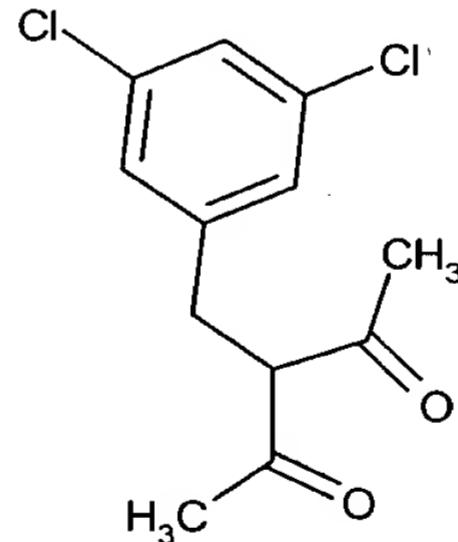
The title compound was prepared by a method similar to that of Preparation 2 using
5 the alkene isomers of Preparation 12 to give the title compound as a 38:62 mixture with its
enol tautomer as estimated by $^1\text{H-NMR}$ as a yellow oil.

$^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 1.06 (d, 6H, diketone and enol), 2.06 (s, 3H, enol),
2.16 (s, 3H, diketone), 2.55 (heptet, 1H, diketone), 2.73 (heptet, 1H, enol), 3.08 (dd, 1H,
diketone), 3.16 (dd, 1H, diketone), 3.68 (s, 2H, enol), 4.10 (t, 1H, diketone), 6.89 (m, 3H,
10 diketone and enol), 7.27 (m, 1H, diketone and enol).

LRMS (electrospray): m/z [MNa $^+$] 259.

PREPARATION 4

3-(3,5-Dichlorobenzyl)-2,4-pentanedione



15 To a solution of the alkene of Preparation 9 (6.4g, 24.9mmol) in ethanol (100ml) and
ethyl acetate (40ml) was added 5% palladium on barium sulphate (640mg) and the resulting
mixture was stirred under an atmosphere of hydrogen (103.4kPa, 15 psi) for 18 hours. The
mixture was filtered through a filter aid (Arbocel (Trade Mark))(caution - fire hazard) under
nitrogen and the filtrate was concentrated under reduced pressure. The residue was purified
20 by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate
(10:1, by volume) and then pentane:ethyl acetate (7:1, by volume) to give the title compound
(5.3g) as a mixture with its enol tautomer as shown by $^1\text{H-NMR}$ as a yellow powder, m.p. 85-
87°C.

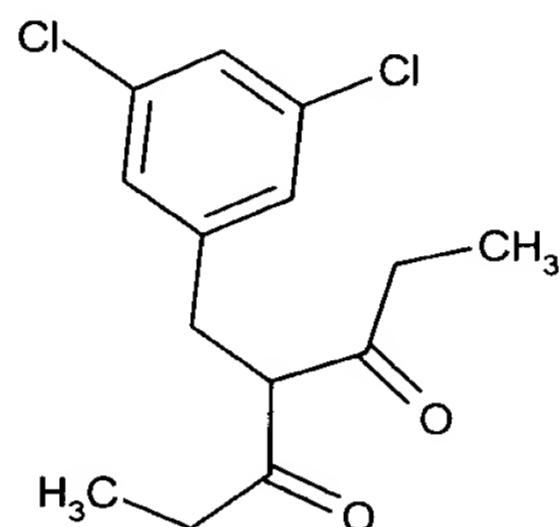
¹H-NMR (400MHz, CDCl₃): δ = 2.02 (s, 6H, enol), 2.15 (s, 6H, diketone), 3.06 (d, 2H, diketone), 3.60 (s, 2H, enol), 3.93 (t, 1H, diketone), 7.00 (s, 2H, enol), 7.03 (s, 2H, diketone), 7.21 (s, 1H, diketone and enol), 16.78 (s, 1H, enol).

5 LRMS (electrospray): m/z [M-H⁺] 257.

Microanalysis: Found: C, 55.91; H, 4.72. C₁₂H₁₂Cl₂O₂ requires C, 55.62; H, 4.67.

PREPARATION 5

4-(3,5-Dichlorobenzyl)-3,5-heptanedione



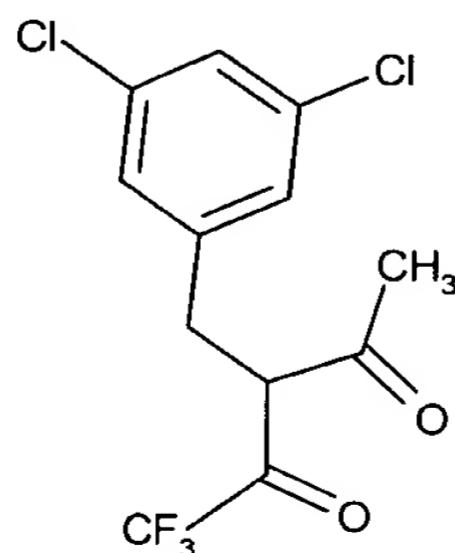
10

The title compound was prepared by a method similar to that of Preparation 1, Method B using the alkene of Preparation 14 and purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate (20:1, by volume) and then pentane:ethyl acetate (10:1, by volume) to give the title compound as a mixture with its enol tautomer as estimated by ¹H-NMR and as an orange oil. A small amount (ca.10%) of dechlorinated impurities presumably arising from over reduction were detected by ¹H-NMR. This over reduction could probably be avoided by using the alternative reduction procedure of Preparation 6.

15 ¹H-NMR (400MHz, CDCl₃): δ = 1.00 (m, 6H, diketone and enol), 2.40 (m, 4H, diketone and enol), 3.11 (d, 2H, diketone), 3.64 (d, 2H, enol), 3.97 (t, 1H, diketone), 7.03 (d, 2H), 7.22 (s, 1H), 17.02 (s, 1H, enol).

PREPARATION 6

3-(3,5-Dichlorobenzyl)-1,1,1-trifluoro-2,4-pentanedione



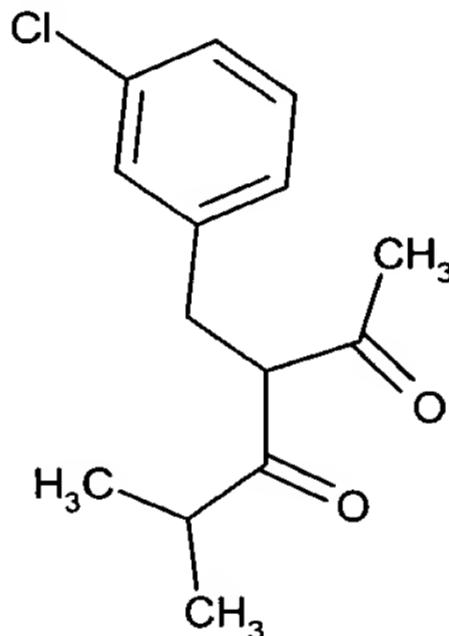
To a solution of a mixture of the alkenes of Preparation 13 (100mg, 0.321mmol) in dichloromethane (3ml) was added diphenylsilane (88.6mg, 0.481mmol), tetrakis(triphenylphosphine)palladium(0) and zinc chloride (8mg, 0.06mmol) and the resulting mixture was stirred under nitrogen at room temperature for 3 days. The mixture was applied 5 directly to a silca gel column and purified by flash chromatography eluting with a solvent gradient of dichloromethane:pentane (1:3, by volume)and then dichloromethane:pentane (1:2, by volume) to give the title compound (78mg) as a mixture with its enol tautomer as shown by $^1\text{H-NMR}$ and as a pale yellow oil.

$^1\text{H-NMR}$ (300MHz, CDCl_3): δ = (enol only, signals for diketone not assigned) 2.14 (s, 10 3H), 3.78 (s, 2H), 7.02 (2, 2H), 7.09 (m, 1H), 16.29 (br. s, 1H).

LRMS (electrospray): m/z [M-H $^+$] 311.

PREPARATION 7

3-(3-Chlorobenzyl)-5-methyl-2,4-hexanedione

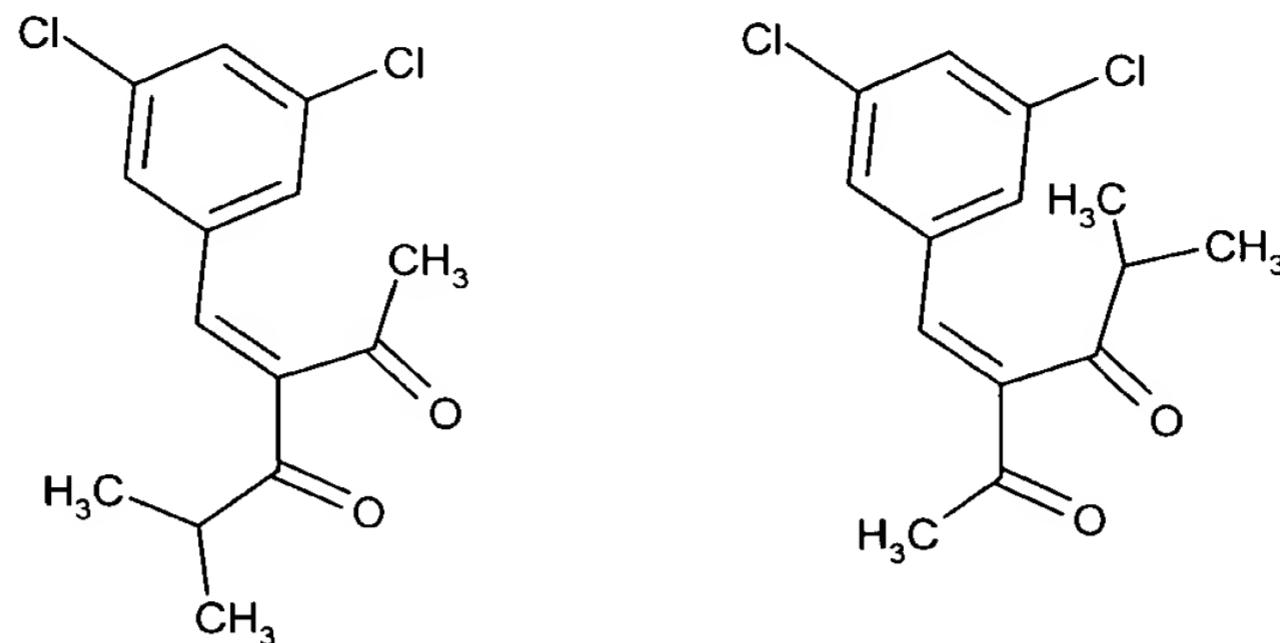


15 The title compound was prepared by a similar method to that of Preparation 6 using a mixture of the alkenes of Preparation 10, being purified by flash chromatography eluting with pentane:ethyl acetate (3:1, by volume) and being obtained as a mixture with its enol tautomer as shown by $^1\text{H-NMR}$ as a yellow oil.

$^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 0.97-1.01 (m, 6H, diketone and enol), 2.02 and 2.10 (2s, 2x3H, diketone and enol), 2.53 and 2.66 (2m, 2x1H, diketone and enol), 3.07 (m, 2H, diketone), 3.61 (s, 2H, enol), 4.05 (m, 1H, diketone), 7.08 (m, 4H, diketone and enol).

PREPARATION 8

(3E)-3-(3,5-Dichlorobenzylidene)-5-methyl-2,4-hexanedione and (3Z)-3-(3,5-dichlorobenzylidene)-5-methyl-2,4-hexanedione



5 A mixture of 5-methyl-2,4-hexanedione (*J. Am. Chem. Soc.*, 1980, 2095-6.) (1.84g, 14.33mmol), 3,5-dichlorobenzaldehyde (2.5g, 14.33mmol), glacial acetic acid (214µL, 3.73mmol), piperidine (29µL, 0.29mmol), dry toluene (10.2ml) and powdered 3Å molecular sieves (100mg) was heated under reflux under nitrogen for 24 hours. A Dean-Stark trap was attached to the reaction and heating under reflux was continued for 3 hours, during which time the toluene evaporated from the reaction. The residue was diluted with dichloromethane (80ml) and filtered to remove molecular sieves. The filtrate was washed with water (80ml), dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with pentane:ether (10:1, by volume) to give the less polar title compound (510.6mg) as a yellow oil.

15 ¹H-NMR (400MHz, CDCl₃): δ = 1.19 (d, 6H), 2.29 (s, 3H), 3.19 (heptet, 1H), 7.24 (s, 2H), 7.34 (s, 1H), 7.40 (s, 1H).

LRMS (thermospray): m/z [MNH₄⁺] 302.

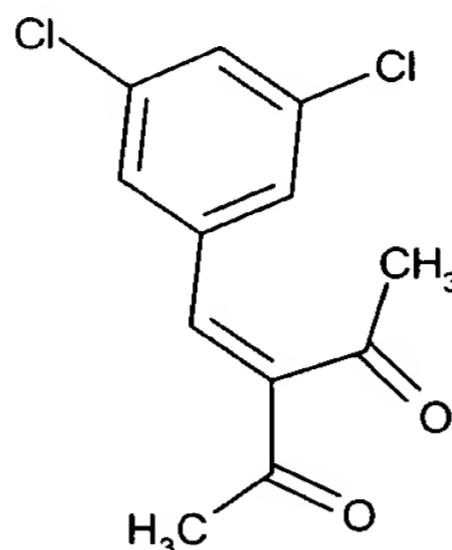
Further elution of the same column gave the more polar title compound (993.3mg) as a yellow oil.

20 ¹H-NMR (400MHz, CDCl₃): δ = 1.05 (d, 6H), 2.40 (s, 3H), 2.58 (heptet, 1H), 7.24 (s, 2H), 7.39 (s, 1H), 7.45 (s, 1H).

LRMS (thermospray): m/z [MNH₄⁺] 302.

PREPARATION 9

3-(3,5-Dichlorobenzylidene)-2,4-pentanedione



Glacial acetic acid (0.49ml, 8.6mmol) and piperidine (57 μ L, 0.6mmol) were added to
5 a stirred solution of 2,4-pentanedione (2.86g, 28.6mmol) and 3,5-dichlorobenzaldehyde
(5.00g, 28.6mmol) in toluene (25ml) and the mixture was heated under reflux using a Dean-
Stark trap for 18 hours. After cooling, the mixture was concentrated under reduced pressure
and the residue was purified by flash chromatography on silica gel eluting with pentane:ethyl
acetate (10:1, by volume) to give the title compound (6.5g) as a red/brown solid, m.p. 85-
10 87°C.

$^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 2.22 (s, 3H), 2.39 (s, 3H), 7.21 (s, 2H), 7.26 (s, 1H),
7.35 (s, 1H).

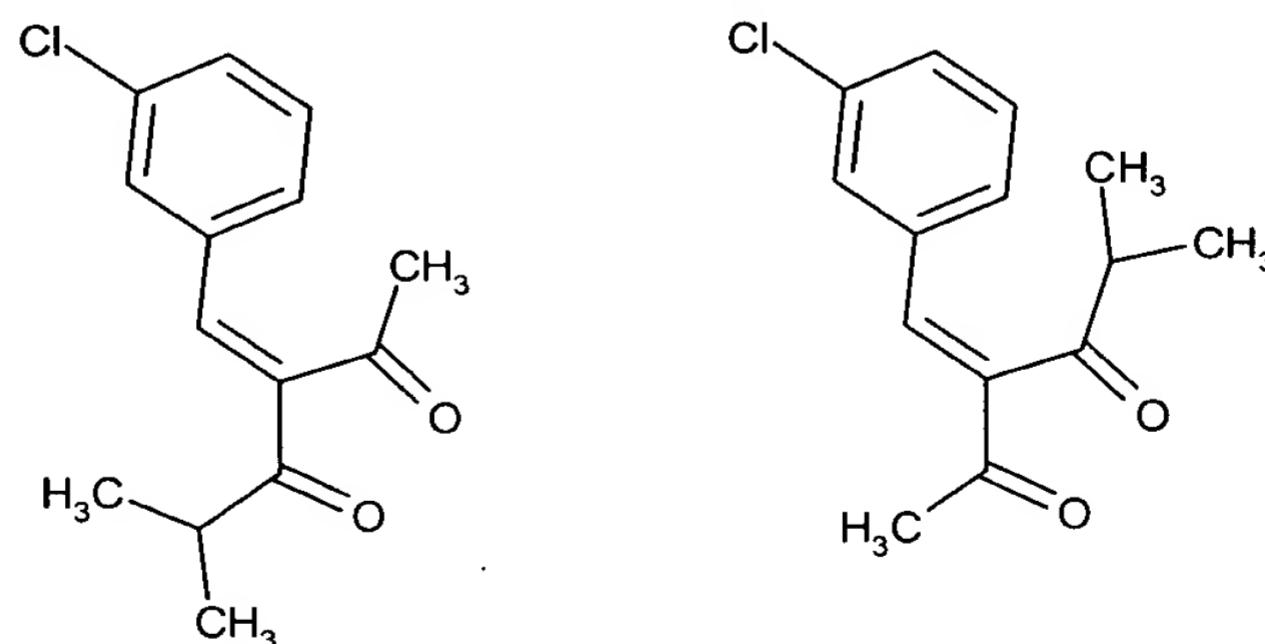
LRMS (thermospray): m/z [MNH₄⁺] 274.

Microanalysis: Found: C, 55.93; H, 3.81. $\text{C}_{12}\text{H}_{10}\text{Cl}_2\text{O}_2$ requires C, 56.06; H, 3.92.

15

PREPARATION 10

(3E)-3-(3-Chlorobenzylidene)-5-methyl-2,4-hexanedione and (3Z)-3-(3-chlorobenzylidene)-5-methyl-2,4-hexanedione



The title compounds were prepared by a similar method to that of Preparation 9 using
20 5-methyl-2,4-hexanedione (*J. Am. Chem. Soc.*, 1980, 2095-6) and 3-chlorobenzaldehyde and
were obtained as yellow oils.

Less polar isomer:

$^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 1.16 (d, 6H), 2.24 (s, 3H), 3.18 (m, 1H), 7.30 (m, 6H).

LRMS (thermospray): m/z [MNH₄⁺] 268.

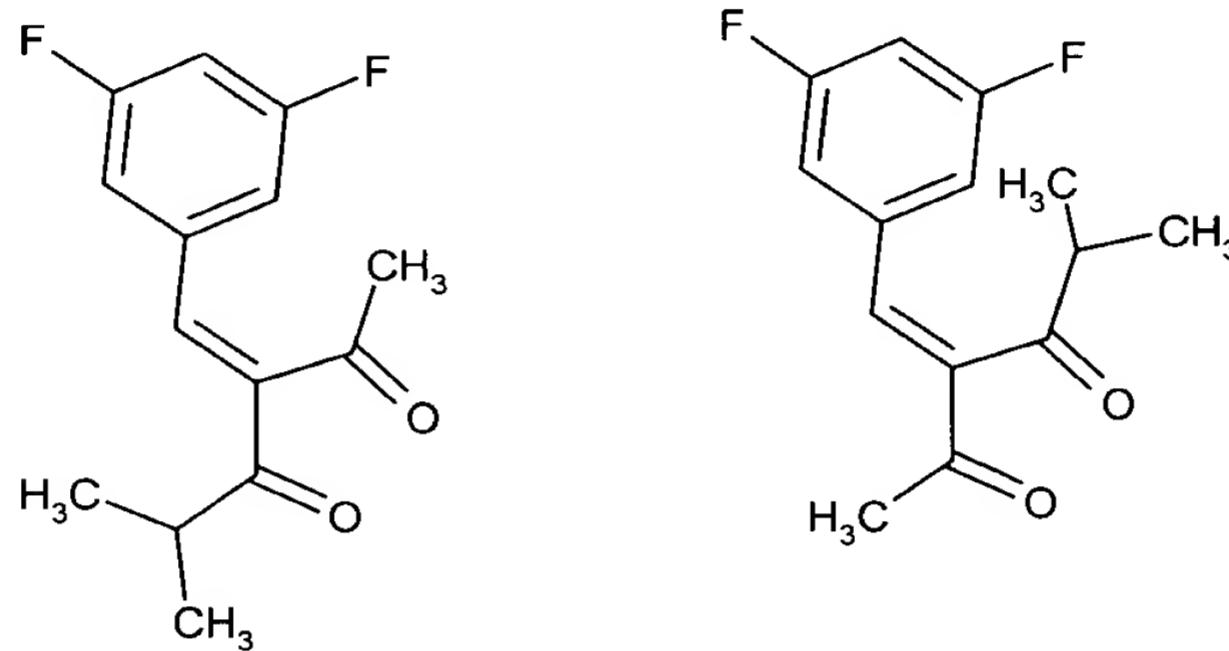
More polar isomer:

¹H-NMR (400MHz, CDCl₃): δ = 1.02 (d, 6H), 2.39 (s, 3H), 2.55 (m, 1H), 7.31 (m, 5H), 7.50 (s, 1H).

5 LRMS (thermospray): m/z [MNH₄⁺] 268.

PREPARATION 11

(3E)-3-(3,5-Difluorobenzylidene)-5-methyl-2,4-hexanedione and (3Z)-3-(3,5-difluorobenzylidene)-5-methyl-2,4-hexanedione



10 The title compounds were prepared by a similar method to that of Preparation 9 using 5-methyl-2,4-hexanedione (*J. Am. Chem. Soc.*, 1980, 2095-6) and 3,5-difluorobenzaldehyde and purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ether (20:1, by volume) and then pentane:ethyl acetate (10:1, by volume) to give the less polar title compound as a yellow oil.

15 Less polar isomer:

¹H-NMR (400MHz, CDCl₃): δ = 1.15 (d, 6H), 2.27 (s, 3H), 3.19 (heptet, 1H), 6.92 (m, 3H), 7.32 (s, 1H).

LRMS (electrospray): m/z [MNH₄⁺] 253.

Further elution of the same column gave the more polar title compound as a yellow oil.

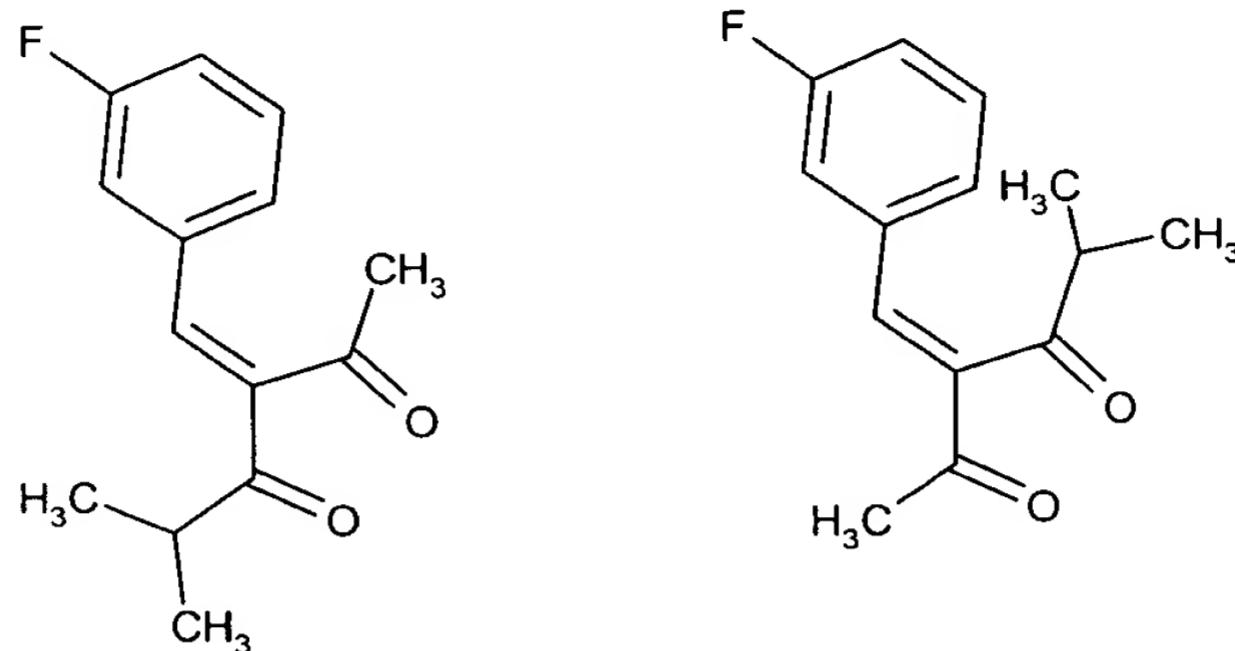
20 More polar isomer:

¹H-NMR (400MHz, CDCl₃): δ = 1.03 (d, 6H), 2.40 (s, 3H), 2.56 (heptet, 1H), 6.96 (m, 3H), 7.44 (s, 1H).

LRMS (electrospray): m/z [MNH₄⁺] 253.

PREPARATION 12

(3E)-3-(3-Fluorobenzylidene)-5-methyl-2,4-hexanedione and (3Z)-3-(3-fluorobenzylidene)-5-methyl-2,4-hexanedione



5 The title compounds were prepared by a similar method to that of Preparation 9 using 5-methyl-2,4-hexanedione (*J. Am. Chem. Soc.*, 1980, 2095-6) and 3-fluorobenzaldehyde and purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ether (20:1, by volume) and then pentane:ethyl acetate (10:1, by volume) to give the less polar title compound as a yellow oil.

10 Less polar isomer:

1H-NMR (300MHz, CDCl₃): δ = 1.23 (d, 6H), 2.29 (s, 3H), 3.24 (heptet, 1H), 7.13 (m, 3H), 7.39 (m, 1H), 7.44 (s, 1H).

LRMS (thermospray): m/z [MNH₄⁺] 235.

Further elution of the same column gave the more polar title compound as a yellow oil.

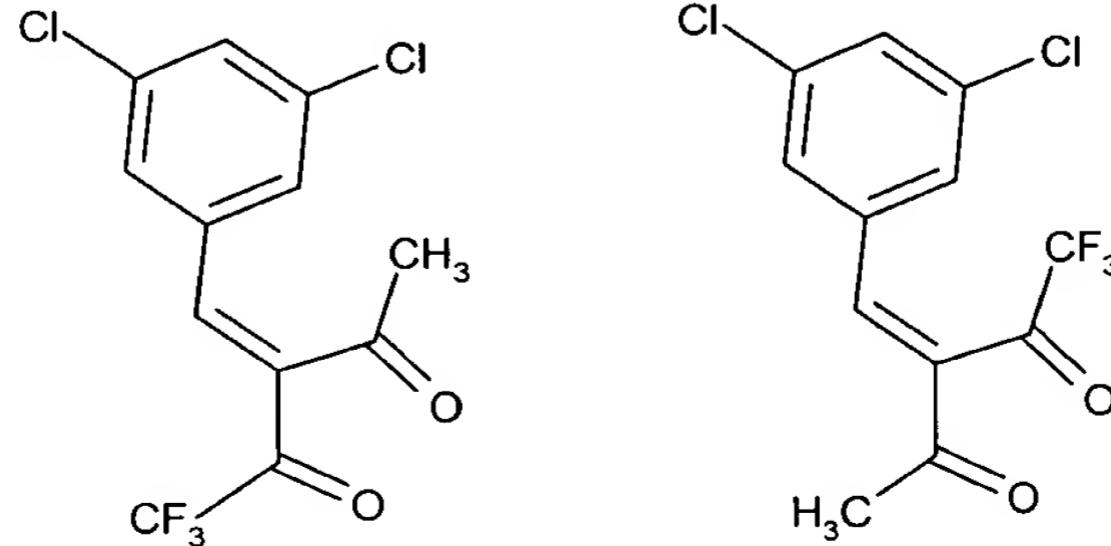
More polar isomer:

1H-NMR (300MHz, CDCl₃): δ = 1.06 (d, 6H), 2.42 (s, 3H), 2.60 (heptet, 1H), 7.11 (m, 3H), 7.35 (m, 1H), 7.55 (s, 1H).

LRMS (thermospray): m/z [MNH₄⁺] 235.

20 PREPARATION 13

(3E)-3-(3,5-Dichlorobenzylidene)-1,1,1-trifluoro-2,4-pentanedione and (3Z)-3-(3,5-dichlorobenzylidene)-1,1,1-trifluoro-2,4-pentanedione

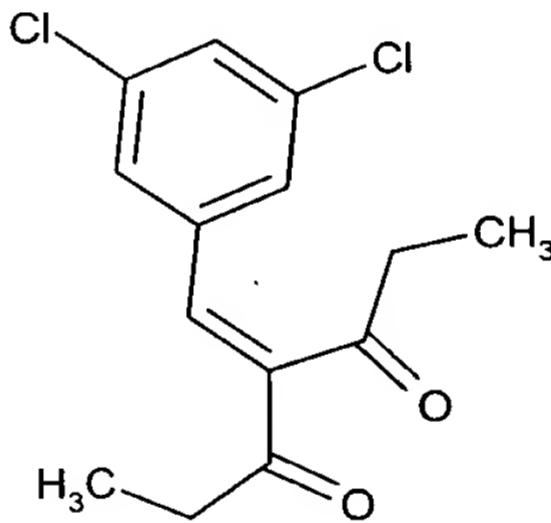


Glacial acetic acid (0.425ml, 7.423mmol) and piperidine (57 μ L, 0.571mmol) were added to a stirred solution of 1,1,1-trifluoro-2,4-pentanedione (4.40g, 28.55mmol) and 3,5-dichlorobenzaldehyde (5.0g, 28.55mmol) in toluene (20ml) and the mixture was heated under reflux using a Dean-Stark trap for 16h. After cooling the mixture was washed with brine (30ml), dried over magnesium sulphate and concentrated under reduced pressure to give a dark brown oil (9.1g) which was purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ether (10:1, by volume), pentane:ether (5:1, by volume) and then dichloromethane:pentane (1:1, by volume) to give the crude products (4.2g) as a brown oil. The crude products were further purified by flash chromatography on silica gel eluting with a solvent gradient of dichloromethane:pentane (1:4, by volume) and then dichloromethane:pentane (1:3, by volume) to give a mixture of the title compounds (683mg) as shown by thin layer chromatography using dichloromethane:pentane (1:1, by volume), major isomer R_f 0.54, minor isomer R_f 0.17, and as a pale yellow oil.

15 $^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 2.49 (s, 3H), 7.23 (s, 2H), 7.46 (s, 1H), 7.66 (s, 1H).
LRMS (electrospray): m/z [MH $^+$] 328.

PREPARATION 14

4-(3,5-Dichlorobenzylidene)-3,5-heptanedione

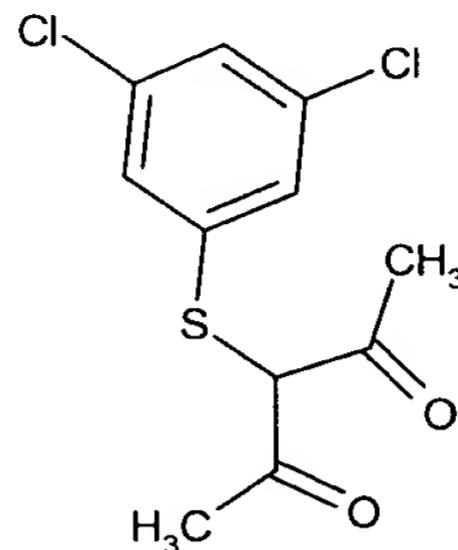


The title compound was prepared by a method similar to that of Preparation 13 using
20 3,5-heptanedione and was purified by chromatography on silica gel eluting with pentane:ether (10:1, by volume) to give a product which was triturated with pentane to give the title compound as a white solid, m.p. 80-82°C.

15 $^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 1.16 (m, 6H), 2.50 (q, 2H), 2.73 (q, 2H), 7.22 (s, 2H), 7.37 (m, 2H).
LRMS (thermospray): m/z [MH $^+$] 285.
Microanalysis: Found: C, 58.97; H, 4.95. $\text{C}_{14}\text{H}_{14}\text{Cl}_2\text{O}_2$ requires C, 58.98; H, 4.93.

Preparation 15

3-[(3,5-Dichlorophenyl)sulfanyl]-2,4-pentanedione



3-Chloro-2,4-pentanedione (723 μ L, 6.07mmol) and then sodium iodide (910mg, 5 6.07mmol) were added to a stirred suspension of 3,5-dichlorothiophenol (1.09g, 6.07mmol) and potassium carbonate (923mg, 6.68mmol) in acetone (30ml), at room temperature, in a flask equipped with a calcium chloride drying tube. The mixture became yellow, then orange and finally red accompanied by a slight exotherm and was stirred for 23 hours at room temperature. The mixture was diluted with water (20ml) and concentrated under reduced pressure in a fumehood (Caution: possible residual lachrymator) to remove acetone. The residue was diluted with 2M hydrochloric acid (20ml) and extracted with dichloromethane (1x40ml, 2x20ml). The combined organic phases were washed with brine (20ml), dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to leave an orange solid (1.66g). The crude product was purified by flash chromatography on silica gel 10 eluting with pentane:diethyl ether (99:1, by volume) to give the title compound (807mg) as a 15 yellow solid m.p. 79-81°C.

$^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 2.30 (2, 6H), 6.91 (s, 2H), 7.09 (s, 1H).

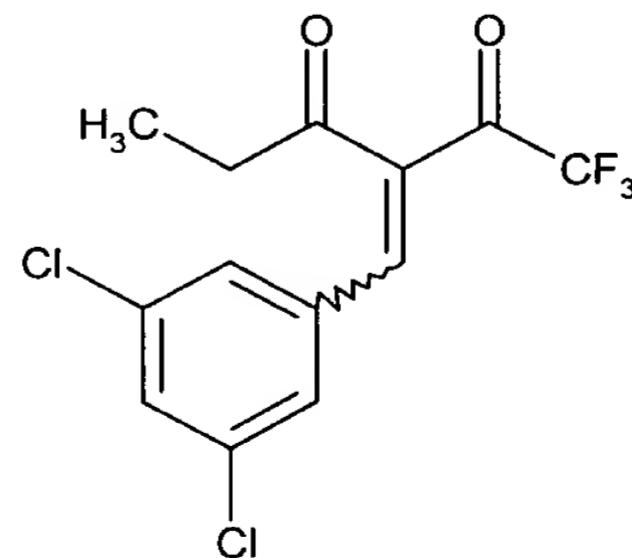
LRMS (thermospray): m/z [MNH₄⁺] 294.

Microanalysis: Found: C, 47.45; H, 3.54; $\text{C}_{11}\text{H}_{10}\text{Cl}_2\text{O}_2\text{S}$ requires C, 47.67; H, 3.64%.

20

Preparation 16

(3E and 3Z)-3-(3,5-Dichlorobenzylidene)-1,1,1-trifluoro-2,4-hexanedione



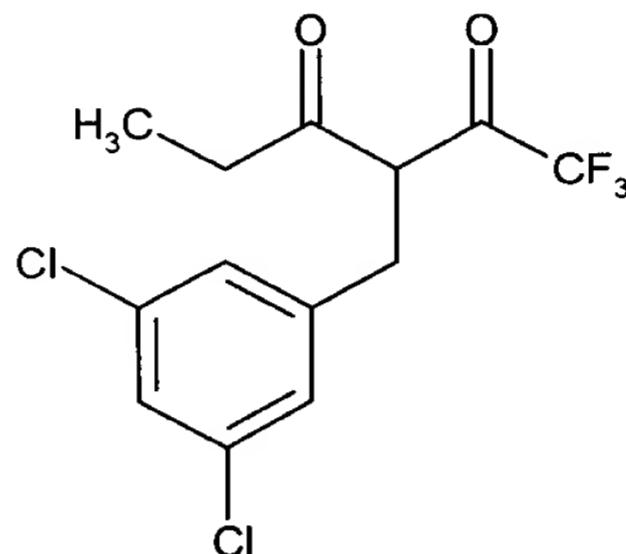
The title compound was prepared by a similar method to that of Preparation 9 using 1,1,1-trifluorohexane-2,4-dione and 3,5-dichlorobenzaldehyde. The crude product was

purified by flash chromatography on silica gel eluting with a solvent gradient of pentane gradually changing to pentane:ethyl acetate (5:1, by volume). The product was further purified by flash chromatography eluting with dichloromethane:pentane (1:10, by volume) to afford a mixture of the title compounds (500mg) as a yellow oil.

5 ¹H-NMR (300MHz, CDCl₃): δ = 1.23 (t, 3H), 2.80 (q, 2H), 7.32 (s, 2H), 7.52 (s, 1H), 7.74 (s, 1H).

Preparation 17

3-(3,5-Dichlorobenzyl)-1,1,1-trifluoro-2,4-hexanedione

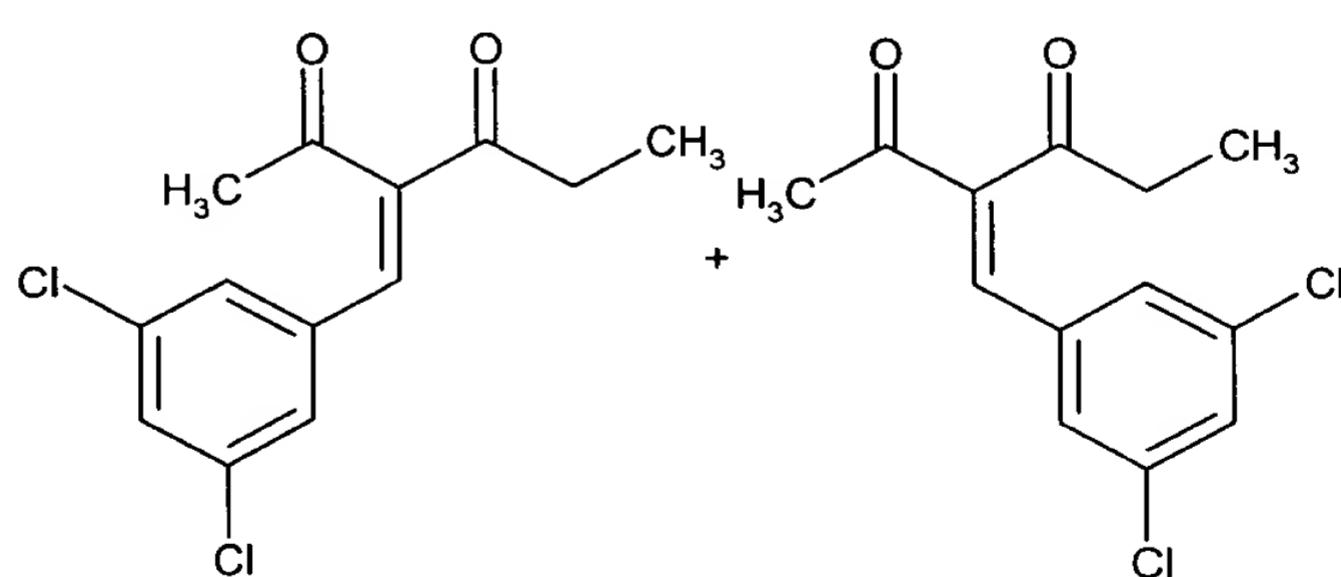


10 The title compound was prepared by a similar method to that of Preparation 6 using 3-(3,5-dichlorobenzylidene)-1,1,1-trifluoro-2,4-hexanedione of Preparation 16 and was obtained as an oily white solid (180mg).

LRMS (thermospray): m/z [MH⁺] 325.

Preparations 18 and 19

15 (3Z)-3-(3,5-Dichlorobenzylidene)-2,4-hexanedione and (3E)-3-(3,5-Dichlorobenzylidene)-2,4-hexanedione



The title compounds were prepared by a similar method to that of Preparation 9 using 2,4-hexanedione and 3,5-dichlorobenzaldehyde. The crude products were purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ether (20:1, by volume) gradually changing to pentane:ether (10:1, by volume) to afford the title compounds as white solids.

Less polar isomer:

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¹H-NMR (300MHz, CDCl₃): δ = 1.10 (t, 3H), 2.40 (s, 3H), 2.52 (q, 2H), 7.20 (s, 2H), 7.39 (s, 1H), 7.40 (s, 1H).

Microanalysis: Found: C, 57.07; H, 4.40. C₁₃H₁₂Cl₂O₂ requires C, 57.59; H, 4.46.

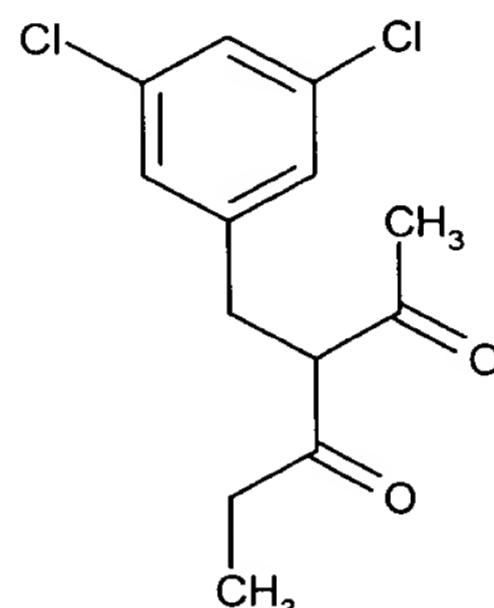
More polar isomer:

5 ¹H-NMR (300MHz, CDCl₃): δ = 1.16 (t, 3H), 2.29 (s, 3H), 2.77 (q, 2H), 7.29 (s, 2H), 7.39 (s, 1H), 7.40 (s, 1H).

Microanalysis: Found: C, 57.21; H, 4.22. C₁₃H₁₂Cl₂O₂ requires C, 57.59; H, 4.46.

Preparation 20

3-(3,5-Dichlorobenzyl)-2,4-hexanedione



10

The title compound was prepared by a similar method to that of Preparation 6 using (3Z)-3-(3,5-dichlorobenzylidene)-2,4-hexanedione and (3E)-3-(3,5-dichlorobenzylidene)-2,4-hexanedione of Preparations 18 and 19 and was obtained as yellow oil (300mg).

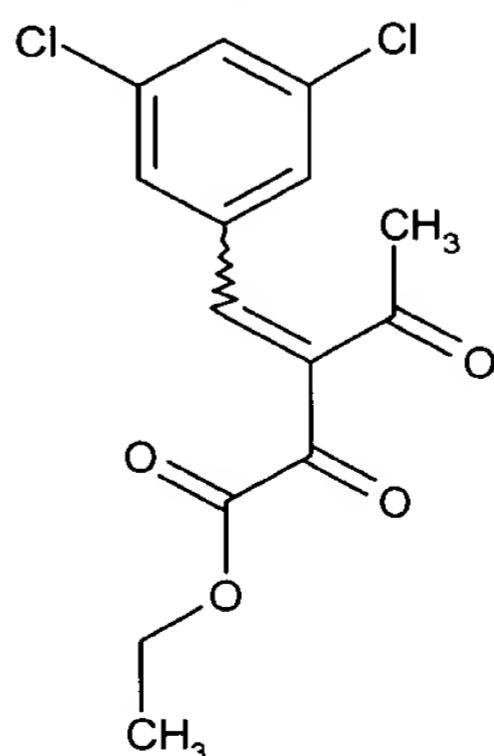
15 ¹H-NMR (300MHz, CDCl₃): (5:4 keto tautomer:enol tautomer) δ = 1.00 (t, 3H, keto), 1.13 (t, 3H, enol), 2.06 (s, 3H, enol), 2.16 (s, 3H, keto), 2.35 and 2.52 (2xm, 2x2H, keto and enol), 3.13 (d, 2H, keto), 3.65 (s, 2H, enol), 3.96 (t, 1H, keto), 7.00 (m, 2x2H, keto and enol), 7.20 (s, 2x1H, keto and enol), 16.87 (s, 1H, enol).

LRMS (thermospray): m/z [MNa⁺] 295.

Preparation 21

20

Ethyl (3E and 3Z)-3-acetyl-4-(3,5-dichlorophenyl)-2-oxo-3-butenoate

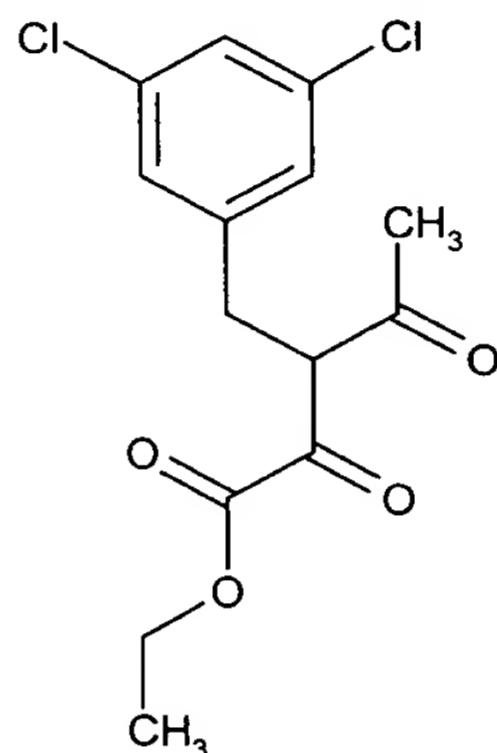


The title compounds were prepared by a similar method to that of Preparation 9 using ethyldioxovalerate and 3,5-dichlorobenzaldehyde and a mixture was obtained (2:3 ratio of isomers, stereochemistry unknown) as an orange oil.

5 $^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 1.25 (m, 3H), 1.29 (m, 3H), 2.37 (s, 3H), 2.44 (s, 3H),
4.21 (q, 2H), 4.30 (q, 2H), 7.21 (s, 2H), 7.22 (s, 2H), 7.40 (s, 1H), 7.41 (s, 1H), 7.68 (s, 2x1H).
LRMS (thermospray): m/z [MNH₄⁺] 332.

Preparation 22

Ethyl 3-(3,5-dichlorobenzyl)-2,4-dioxopentanoate

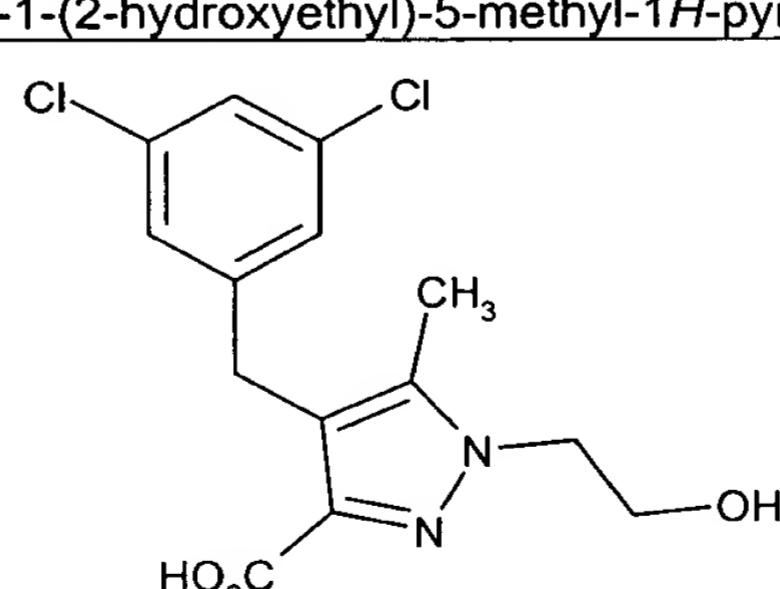


10 The title compound was prepared by a similar method to that of Preparation 6 using ethyl (3*E* and 3*Z*)-3-acetyl-4-(3,5-dichlorophenyl)-2-oxo-3-butenoate of Preparation 21 and was obtained as a yellow oil (8.2g).

15 $^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 1.19 (m, 3H), 1.31 (m, 3H), 2.12 (s, 3H), 2.20 (s, 3H),
2.98 (dq, 1H, diketone), 3.74 (s, 2H, enol), 4.23 (m, 4H), 7.03 (s, 4H), 7.20 (s, 2H), 15.91 (s,
1H).
LRMS (thermospray): m/z [MH⁺] 317.

Preparation 23

4-(3,5-Dichlorobenzyl)-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazole-3-carboxylic acid



20 A solution of the ester of Example 84 (1.0g, 2.8mmol) in 1,4-dioxan (14ml) was treated with 1M aqueous sodium hydroxide solution (7ml) and the reaction mixture was stirred at room temperature for 4 hours. The solution was concentrated under reduced pressure. The

residue was dissolved in water (25ml) and 2M aqueous hydrochloric acid was added. A precipitate formed and was filtered off to afford the title compound as a white solid (613mg), m.p. 241.2-242.4°C. Further product was obtained from the filtrate by adding methanol and concentrating the solvents under reduced pressure. The residue was dissolved in water and aqueous hydrochloric acid added. A precipitate formed and was filtered off to afford a white solid (108mg).

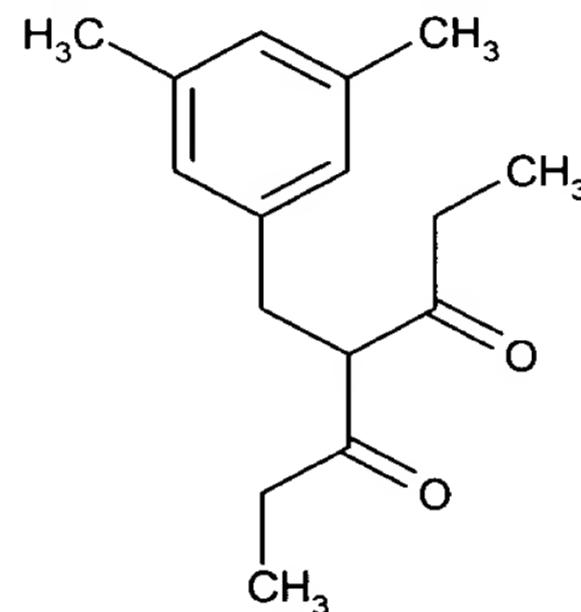
5 $^1\text{H-NMR}$ (300MHz, $\text{d}_6\text{-DMSO}$): δ = 2.20 (s, 3H), 3.69 (s, 2H), 4.01 (m, 2H), 4.13 (m, 2H), 7.19 (s, 2H), 7.38 (s, 1H).

LRMS (electrospray): m/z [MH $^+$] 327.

10

Preparation 24

4-(3,5-Dimethylbenzyl)-3,5-heptanedione



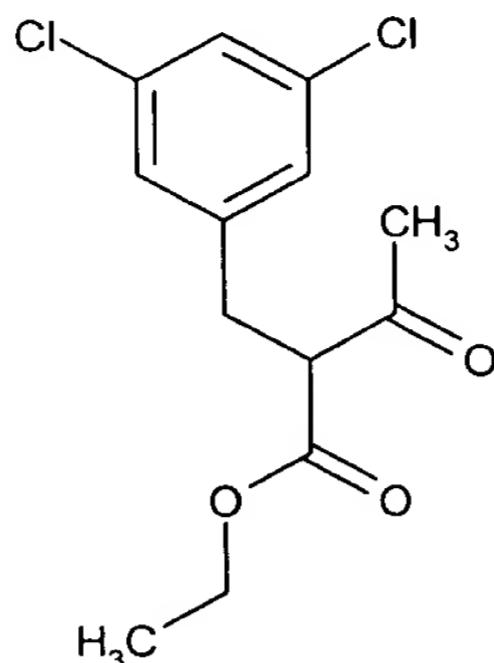
A solution of 3,5-heptanedione (1.24ml, 9.13mmol) in 2-butanone (40ml) was treated with sodium hydride (60% dispersion in oil) (402mg, 10.05mmol) (added in portions) and 15 stirred at room temperature for 10 minutes. Sodium iodide (1.5g, 10.05mmol) and then 3,5-dimethylbenzyl bromide (2.0g, 10.05mmol) were added to the reaction mixture which was stirred at room temperature for 18 hours. The solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water (x3). The organic phase was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced 20 pressure. The crude product was purified by flash chromatography on silica gel eluting with cyclohexane followed by cyclohexane:ethyl acetate (40:1, by volume) to afford the title compound as a yellow oil (995mg).

25 $^1\text{H-NMR}$ (300MHz, CDCl_3): (1.7:1 keto tautomer:enol tautomer) δ = 1.00 (t, 6H, keto), 1.10 (t, 6H, enol), 2.28 (s, 6H, keto), 2.30 (s, 6H, enol), 2.40 (m, 2x4H, keto and enol), 3.10 (d, 2H, keto), 3.61 (s, 2H, enol), 4.00 (t, 1H, keto), 6.77 (s, 2x2H, keto and enol), 6.87 (s, 2x1H, keto and enol), 16.97 (s, 1H, enol).

LRMS (thermospray): m/z [MH $^+$] 247.

Preparation 25

Ethyl 2-(3,5-dichlorobenzyl)-3-oxobutanoate



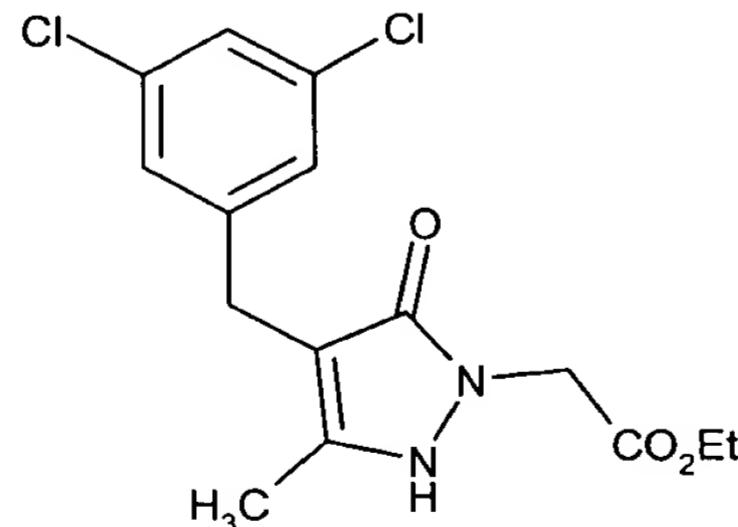
Sodium metal (1.01g, 44mmol) was added to ethanol (100ml) and stirred until all the metal had dissolved. Ethylacetoacetate (15.6g, 111mmol) was added and the reaction mixture was stirred under a nitrogen atmosphere for 10 minutes. 3,5-dichlorobenzyl chloride (7.24g, 40mmol) was added and the reaction mixture was stirred at room temperature for 3 days. The reaction mixture was filtered and the solution was concentrated under reduced pressure. The orange oil was purified by flash chromatography on silica gel eluting with pentane followed by pentane:ethyl acetate (30:1, by volume) to afford the title compound as a colourless oil (6.4g).

15 ¹H-NMR (300MHz, CDCl₃): (3.3:1 keto tautomer:enol tautomer) δ = 1.23 (t, 2x3H, keto and enol), 2.10 (s, 3H, enol), 2.26 (s, 3H, keto), 3.13 (m, 2H, keto), 3.55 (s, 2H, enol), 3.74 (t, 1H, keto), 4.23 (q, 2H, keto and enol), 7.10 (s, 2H, enol), 7.13 (s, 2H, keto), 7.20 (s, 1H, enol), 7.29 (s, 1H, keto), 12.97 (s, 1H, enol).

LRMS (thermospray): m/z [MNH₄⁺] 306, 308.

Preparation 26

Ethyl [4-(3,5-dichlorobenzyl)-3-methyl-5-oxo-2,5-dihydro-1*H*-pyrazol-1-yl]acetate



A solution of the β-ketoester of Preparation 25 (100mg, 0.35mmol) in ethanol (2ml) 20 was treated with triethylamine (53μL, 0.38mmol) and by ethyl hydrazinoacetate hydrochloride (54mg, 0.35mmol) and the resulting mixture was heated at 80°C in a sealed Reacti-vial (Trade Mark) for 18 hours. After cooling, the mixture was concentrated under reduced pressure. The residue was partitioned between aqueous saturated sodium hydrogen

carbonate solution and dichloromethane. The organic phase was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The resulting solid was purified by flash chromatography on silica gel eluting with methanol:dichloromethane (1:99, by volume) to afford the title compound (40mg) as a white solid, m.p. 183.1-184.4°C.

5 ¹H-NMR (300MHz, CDCl₃): δ = 1.20 (t, 3H), 1.97 (s, 3H), 3.45 (brs, 1H), 3.52 (s, 2H), 4.16 (q, 2H), 4.48 (s, 2H), 7.06 (s, 2H), 7.13 (s, 1H).

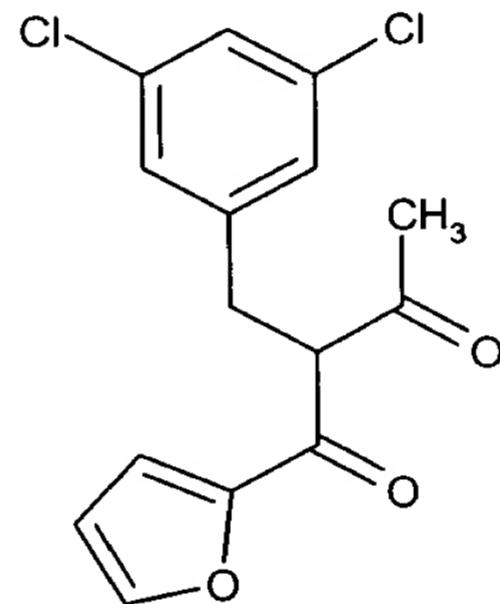
LRMS (thermospray): m/z [MH⁺] 343.

Microanalysis: Found: C, 52.39; H, 4.68; N, 8.08. C₁₅H₁₆Cl₂N₂O₃ requires C, 52.49; H, 4.70; N, 8.16%.

10

Preparation 27

2-(3,5-Dichlorobenzyl)-1-(2-furyl)-1,3-butanedione



The title compound was prepared by a similar method to that of Preparation 24 using 1-(2-furyl)-1,3-butanedione except that the reaction mixture was heated at 85°C. The crude 15 product was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (10:1, by volume) to afford the title compound (1.8g) as a yellow oil.

1H-NMR (400MHz, CDCl₃): δ = 2.13 (s, 3H), 3.17 (d, 2H), 4.54 (t, 1H), 6.57 (m, 1H), 7.05 (s, 2H), 7.12 (s, 1H), 7.22 (m, 1H), 7.60 (m, 1H).

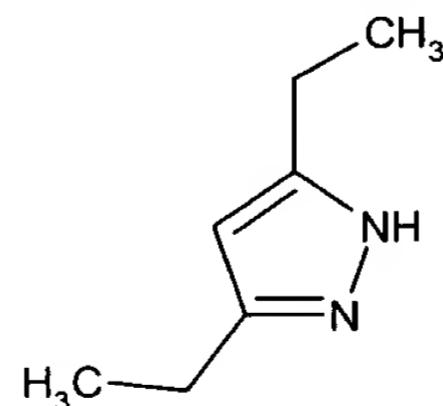
LRMS (thermospray): m/z [MH⁺] 312.

20

Microanalysis: Found: C, 57.85 H, 4.23. C₁₅H₁₂Cl₂O₃ requires C, 57.90; H, 3.89.

Preparation 28

3,5-Diethyl-1*H*-pyrazole



A solution of 3,5-heptanedione (10.0g, 0.078mmol) in ethanol (40ml) was treated 25 dropwise with hydrazine hydrate (4.2ml, 0.086mmol) at room temperature producing an

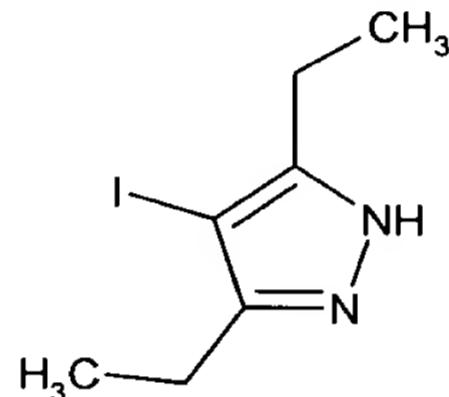
exotherm that was cooled by use of an ice bath. After the addition was complete the reaction mixture was allowed to warm to room temperature. The solution was concentrated under reduced pressure. The oil was partitioned between dichloromethane and brine. The aqueous layer was extracted with dichloromethane (x2). The combined organic phases were dried over 5 anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to afford the title compound (9.66g) as a pale yellow oil that partly solidified on standing.

¹H-NMR (400MHz, CDCl₃): δ = 1.22 (t, 6H), 2.60 (q, 4H), 5.85 (s, 1H).
LRMS (thermospray): m/z [MH⁺] 124.

Microanalysis: Found: C, 67.00 H, 9.85; N, 22.37. C₇H₁₂N₂ requires C, 66.73; H, 9.76; 10 N, 22.23%.

Preparation 29

3,5-Diethyl-4-iodo-1*H*-pyrazole



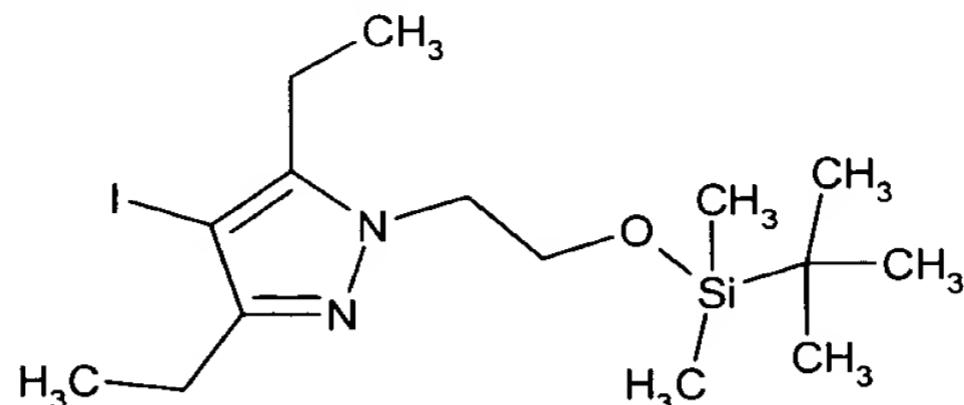
A solution of the pyrazole of Preparation 28 (2.0g, 16.1mmol) in dichloromethane 15 (80ml) was cooled to 0°C and treated with N-iodosuccinimide (3.97g, 17.7mmol) and the resulting mixture was stirred for 18 hours. Further N-iodosuccinimide (360mg, 1.77mmol) was added and the solution was stirred for a further hour. The reaction mixture was washed with saturated aqueous sodium hydrogencarbonate solution. The organic layer was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude 20 product was purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate (4:1, by volume) gradually changing to pentane:ethyl acetate (2:1, by volume). Methanol was added to the resulting solid, which was collected by filtration and the filtrate was concentrated under reduced pressure. The resulting oil was dissolved in dichloromethane and washed with 10% aqueous sodium metabisulphite solution. The organic 25 layer was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to afford the title compound (3.3g) as a white solid.

¹H-NMR (400MHz, CDCl₃): δ = 1.26 (t, 6H), 2.68 (q, 4H).
LRMS (thermospray): m/z [MH⁺] 251.

Microanalysis: Found: C, 33.41 H, 4.38; N, 11.14. C₇H₁₁N₂I requires C, 33.62; H, 30 4.43; N, 11.20%.

Preparation 30

1-(2-{{[tert-Butyl(dimethyl)silyl]oxy}ethyl}-3,5-diethyl-4-iodo-1*H*-pyrazole



A solution of the pyrazole of Preparation 29 (3.3g, 13.2mmol) in dimethylformamide
5 (70ml) was cooled to 0°C and treated with sodium hydride (60% dispersion in oil) (580mg,
14.5mmol). After 20 minutes sodium iodide (2.17g, 14.5mmol) and (2-bromoethoxy)-tert-
butyldimethylsilane (3.11ml, 14.5mmol) were added and the resulting mixture was stirred at
0°C for 30 minutes. The reaction mixture was allowed to warm to room temperature and was
stirred for 18 hours at this temperature. Further (2-bromoethoxy)-tert-butyldimethylsilane
10 (2x2.8ml) was added over a 2 hour period. The reaction mixture was then heated at 50°C for
1 hour. After cooling to 0°C, the reaction mixture was diluted with water (2ml) and evaporated
under reduced pressure. The resulting solid was partitioned between dichloromethane and
water. The organic layer was dried over anhydrous magnesium sulphate, filtered and
evaporated under reduced pressure. The resulting oil was then dissolved in ethyl acetate and
15 washed with brine (x4). The organic phase was dried over anhydrous magnesium sulphate,
filtered and evaporated under reduced pressure. The crude product was purified by flash
chromatography on silica gel eluting with a solvent gradient of cyclohexane gradually
changing to cyclohexane:ethyl acetate (10:1, by volume) to afford the title compound (2.6g)
as a colourless oil.

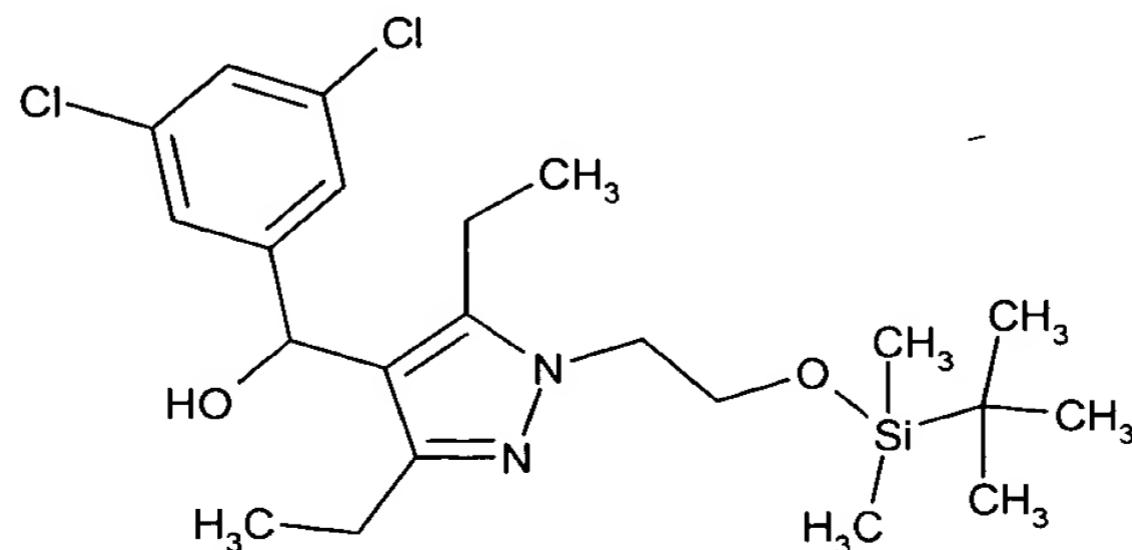
20 $^1\text{H-NMR}$ (400MHz, CDCl_3): $\delta = -0.10$ (s, 6H), 0.80 (s, 9H), 1.16 (t, 3H), 1.23 (t, 3H),
2.60 (q, 2H), 2.74 (q, 2H), 3.97 (t, 2H), 4.16 (t, 2H).

LRMS (thermospray): m/z [MH $^+$] 409.

Preparation 31

[1-(2-{{[tert-Butyl(dimethyl)silyl]oxy}ethyl}-3,5-diethyl-1*H*-pyrazol-4-yl](3,5-

25 dichlorophenyl)methanol



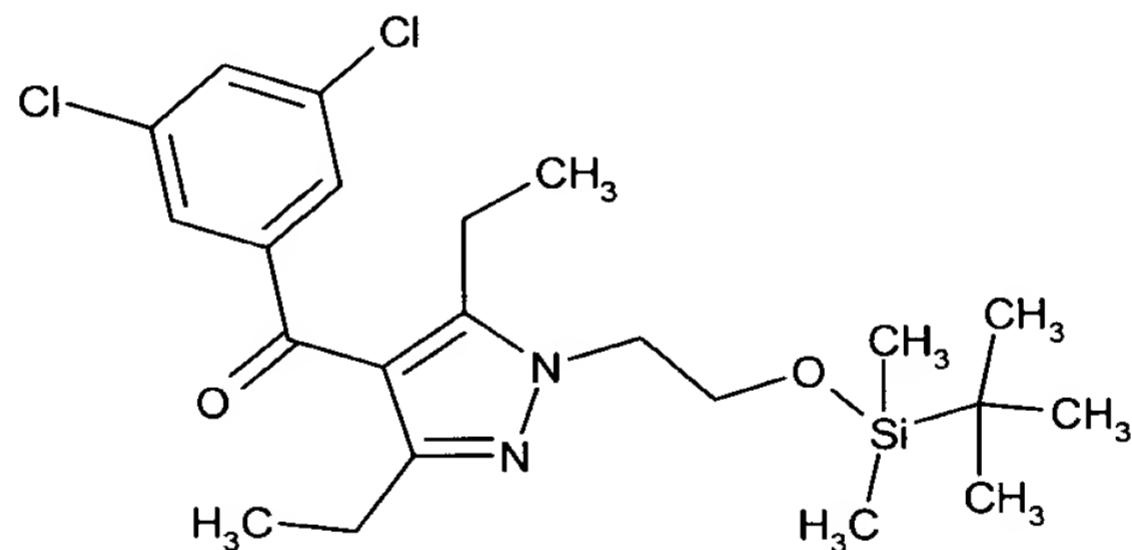
A solution of the iodo-pyrazole (500mg, 1.22mmol) of Preparation 30 in tetrahydrofuran (7.5ml) at 0°C was treated with iso-propylmagnesium chloride (2M in diethylether) (725µL, 1.46mmol). After 1 hour, 3,5-dichlorobenzaldehyde (252mg, 1.46mmol) was added and after a further 10 minutes the reaction mixture was allowed to warm to room temperature. After 3 days saturated aqueous ammonium chloride solution was added to the reaction mixture which was then extracted with dichloromethane. The organic extract was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate (5:1, by volume) gradually changing to pentane:ethyl acetate (2:1, by volume) to afford the title compound (190mg) as a white solid.

¹H-NMR (400MHz, CDCl₃): δ = -0.10 (s, 6H), 0.80 (s, 9H), 1.03 (t, 3H), 1.16 (t, 3H), 2.58 (m, 4H), 4.00 (t, 2H), 4.10 (t, 2H), 5.80 (s, 1H), 7.39 (m, 3H).

LRMS (thermospray): m/z [MH⁺] 457.

Preparation 32

15 [1-(2-{{[tert-Butyl(dimethyl)silyl]oxy}ethyl}-3,5-diethyl-1*H*-pyrazol-4-yl](3,5-dichlorophenyl)methanone



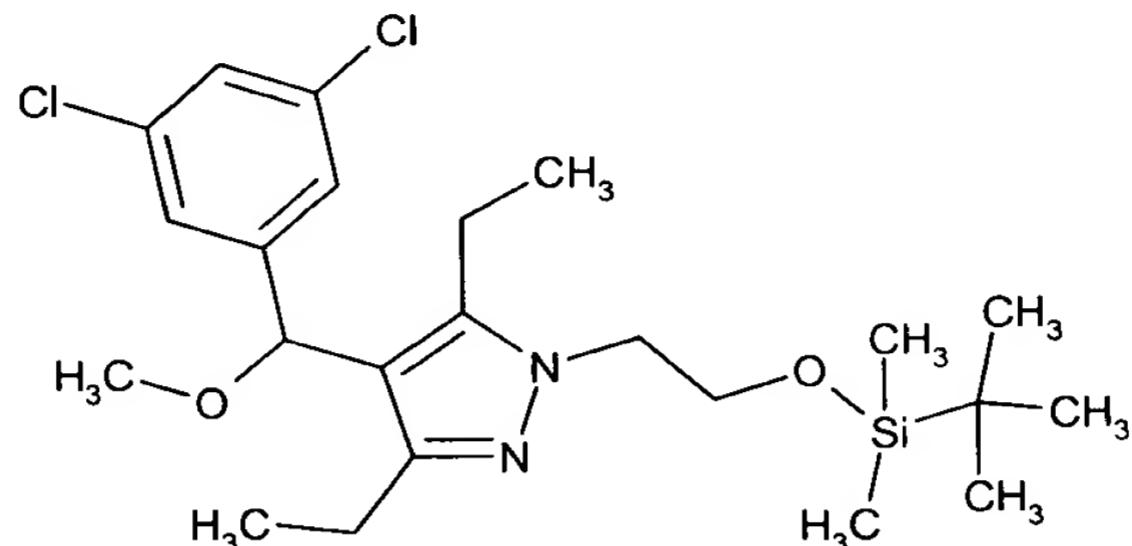
A solution of the alcohol of Preparation 31 (75mg, 0.16mmol) in dichloromethane (2ml) was treated with *N*-methylmorpholine *N*-oxide (28mg, 0.24mmol) and tetra-n-propylammonium perruthenate (VII) (3mg, 0.008mmol) and stirred at room temperature, under a nitrogen atmosphere for 2 hours. The reaction was diluted with dichloromethane and washed with aqueous sodium sulphite solution (x3). The organic layer was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude material was pre-absorbed onto silica and purified by flash chromatography on silica gel eluting with a solvent gradient of pentane gradually changing to pentane:ethyl acetate (10:1, by volume) to afford the title compound (73mg) as a colourless oil.

¹H-NMR (400MHz, CDCl₃): δ = -0.03 (s, 6H), 0.84 (s, 9H), 1.13 (m, 6H), 2.48 (m, 2H), 2.77 (m, 2H), 4.06 (m, 2H), 4.19 (m, 2H), 7.29 (s, 1H), 7.58 (s, 2H).

LRMS (thermospray): m/z [MH⁺] 455.

Preparation 33

1-(2-{{[Tert-butyl(dimethyl)silyl]oxy}ethyl}-4-[(3,5-dichlorophenyl)(methoxy)methyl]-3,5-diethyl-1*H*-pyrazole



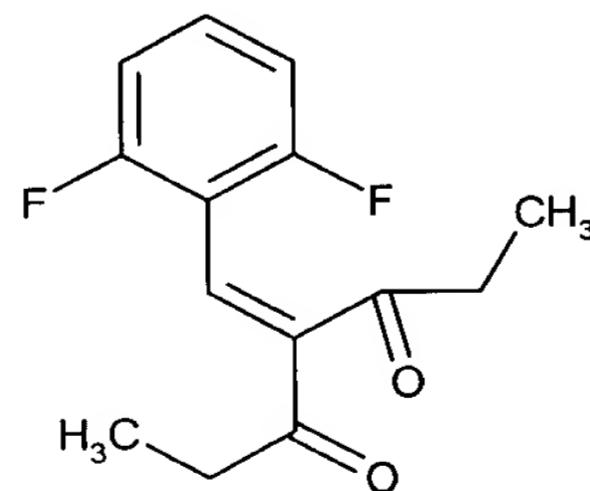
5 A solution of the alcohol of Preparation 31 (75mg, 0.16mmol) in dimethylformamide (1ml) was treated with sodium hydride (60% dispersion in oil) (7mg, 0.18mmol) and stirred under a nitrogen atmosphere, at room temperature for 30 minutes. Methyl iodide (11 μ L, 0.18mmol) was added and the resulting mixture was stirred for 7 days. The solution was concentrated under reduced pressure. The residue was partitioned between dichloromethane and saturated aqueous sodium hydrogencarbonate solution. The organic phase was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (10:1, by volume) to afford the title compound (30mg) as a colourless oil.

10

15 $^1\text{H-NMR}$ (400MHz, CDCl_3): $\delta = -0.10$ (m, 6H), 0.81 (s, 9H), 1.03 (t, 3H), 1.16 (t, 3H), 2.58 (m, 4H), 3.39 (s, 3H), 4.03 (m, 2H), 4.13 (m, 2H), 5.20 (s, 1H), 7.29 (s, 3H).
LRMS (thermospray): m/z [MH $^+$] 471.

Preparation 34

4-(2,6-Difluorobenzylidene)-3,5-heptanedione



20 A mixture of 3,5-heptanedione (1.36ml, 10mmol), 2,6-difluorobenzaldehyde (1.08ml, 10mmol), piperidine (20 μ L, 0.2mmol), glacial acetic acid (149 μ L, 2.6mmol), molecular sieves and toluene (7ml) was heated at 70°C, under a nitrogen atmosphere for 3 hours. Further 2,6-difluorobenzaldehyde (540 μ L, 5mmol) was added and the resulting mixture was stirred at 25 70°C for a further 7 hours. After cooling, the molecular sieves were filtered off. The filtrate was

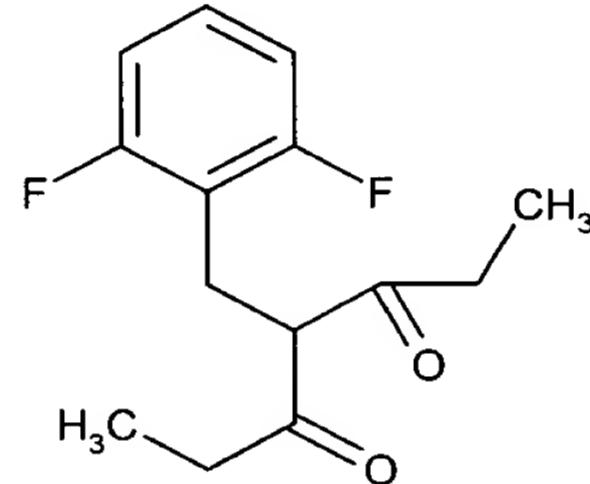
concentrated under reduced pressure. The residue was partitioned between dichloromethane and water. The organic phase was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with pentane:dichloromethane (4:1, by volume) and then 5 with a solvent gradient of pentane:diethylether (20:1, by volume) gradually changing to pentane:diethylether (10:1, by volume) to afford the title compound (775mg) as a colourless oil.

10 $^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 1.11 (t, 3H), 1.20 (t, 3H), 2.63 (q, 2H), 2.80 (q, 2H), 6.95 (m, 2H), 7.40, (s, 1H), 7.65 (m, 1H).

15 LRMS (electrospray): m/z $[\text{MH}^+]$ 253.

Preparation 35

4-(2,6-Difluorobenzyl)-3,5-heptanedione



The title compound was prepared by the same method as Preparation 2 using the 15 alkene of Preparation 34 and was obtained as a white solid, m.p. 55-56°C.

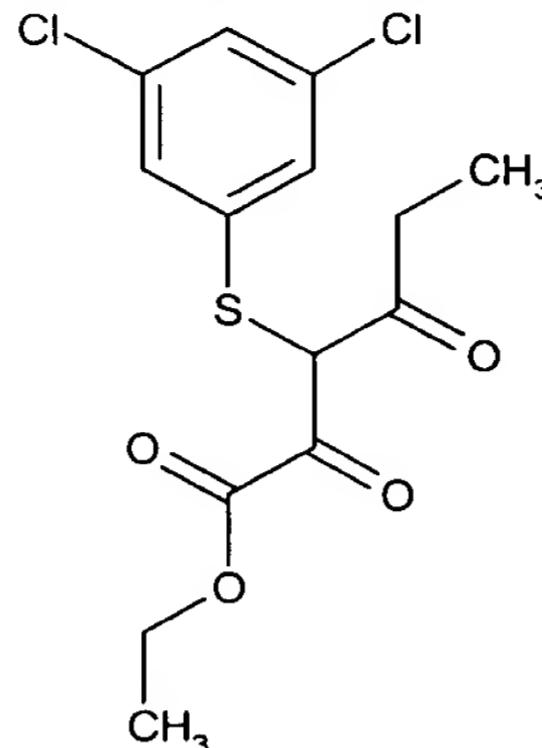
15 $^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 1.00 (t, 6H), 2.46 (m, 4H), 3.20 (d, 2H), 4.03 (t, 1H), 6.84 (m, 2H), 7.18 (m, 1H).

LRMS (thermospray): m/z $[\text{MNH}_4^+]$ 272.

Microanalysis: Found: C, 66.22 H, 6.34. $\text{C}_{14}\text{H}_{16}\text{F}_2\text{O}_2$ requires C, 66.13; H, 6.34.

Preparation 36

Ethyl 3-[(3,5-dichlorophenyl)sulfanyl]-2,4-dioxohexanoate



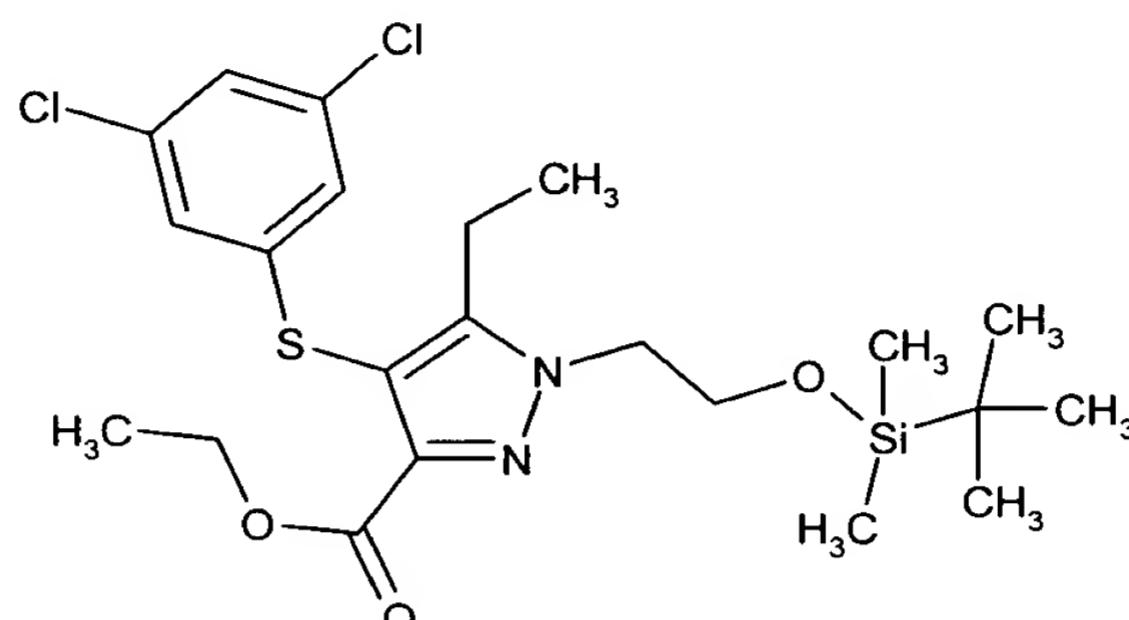
A solution of ethyl 3-chloro-2,4-dioxohexanoate (EP117082 A2) (7.10g, 34.4mmol) in acetone (175ml) was treated with 3,5-dichlorothiophenol (6.16g, 34.4mmol), potassium carbonate (5.22g, 37.8mmol) and sodium iodide (5.16g, 34.4mmol) and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with water (70ml) and concentrated under reduced pressure. The residue was diluted with 2M aqueous hydrochloric acid (70ml) and extracted with dichloromethane (3x150ml). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with a solvent gradient of cyclohexane:ethyl acetate (3:1, by volume) gradually changing to cyclohexane:ethyl acetate (1:1, by volume) to afford the title compound (12.3g) as a red oil.

¹H-NMR (400MHz, CDCl₃): δ = 1.14 (t, 3H), 1.19 (t, 3H), 2.70 (q, 2H), 4.28 (q, 2H), 7.02 (s, 2H), 7.14 (s, 1H), 16.15 (brs, 1H).

LRMS (electrospray): m/z [M-H⁺] 347.

Preparation 37

Ethyl 1-(2-{{tert-butyl(dimethyl)silyl}oxy}ethyl)-4-[(3,5-dichlorophenyl)sulfanyl]-5-ethyl-1*H*-pyrazole-3-carboxylate



5

To a solution of Example 46 (1.03g, 2.65mmol) in dimethylformamide (5ml) was added imidazole (361mg, 5.30mmol), followed by tert-butyldimethylchlorosilane (600mg, 3.97mmol). The solution was stirred at room temperature for 4 days. The reaction mixture was partitioned between ethyl acetate and water and the aqueous phase was further extracted with ethyl acetate. The combined organic phases were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give a yellow oil. The crude product was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (20:1, by volume), followed by cyclohexane:ethyl acetate (5:1, by volume) to afford the title compound (1.1g) as a white powder, m.p. 83-84°C.

15 ¹H-NMR (400MHz, CDCl₃): δ = -0.08 (s, 6H), 0.80 (s, 9H), 1.12 (t, 3H), 1.22 (t, 3H), 2.84 (q, 2H), 4.04 (t, 2H), 4.32 (m, 4H), 6.91 (s, 2H), 7.04 (s, 1H).

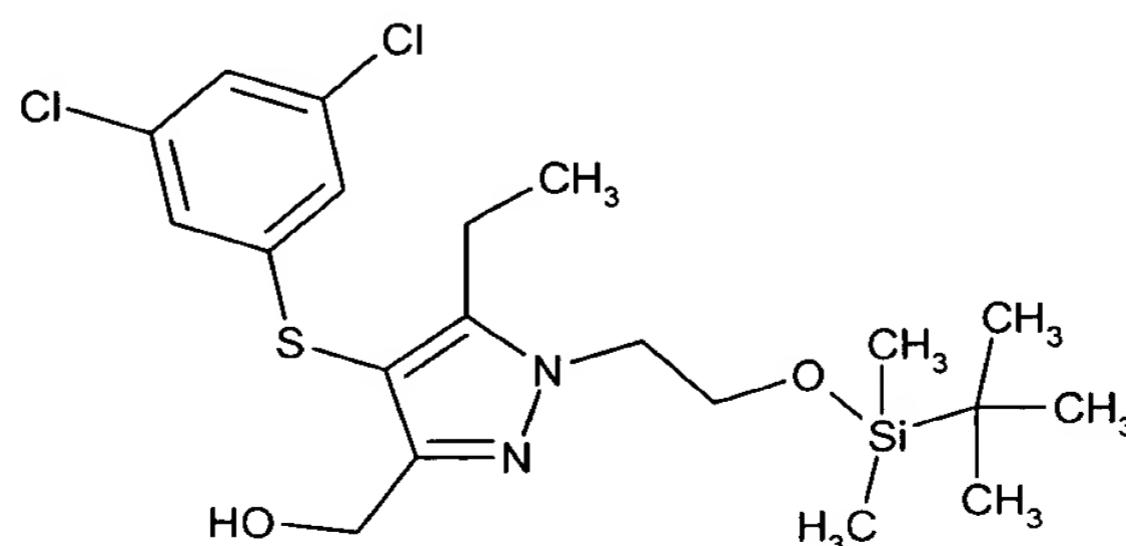
LRMS (thermospray): m/z [MH⁺] 503.

Microanalysis: Found: C, 52.35; H, 6.43; N, 5.46. C₂₂H₃₂Cl₂N₂O₃SSi requires C, 52.47; H, 6.41; N, 5.56%.

20

Preparation 38

{1-(2-{{tert-Butyl(dimethyl)silyl}oxy}ethyl)-4-[(3,5-dichlorophenyl)sulfanyl]-5-ethyl-1*H*-pyrazol-3-yl}methanol



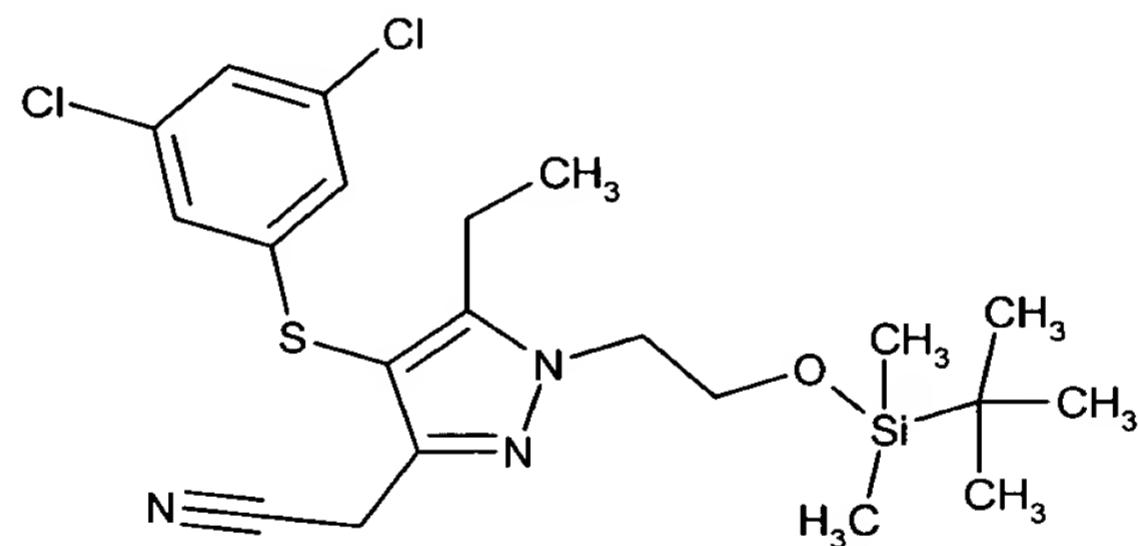
A stirred solution of the pyrazole (1.11g, 2.21mmol) of Preparation 37 in THF (20ml) was cooled to -78°C and treated dropwise with a solution of lithium aluminium hydride in THF (2.65ml of a 1.0M solution). After 1 hour the mixture was warmed to 0°C and after a further 2 hours water (2ml) was carefully added. The reaction mixture was partitioned between ethyl acetate and water and then the aqueous phase was further extracted with ethyl acetate. The combined organic phases were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give a colourless oil. The crude product was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (10:1, by volume) followed by cyclohexane:ethyl acetate (5:1, by volume) to afford the title compound (891mg) as a colourless oil.

¹H-NMR (400MHz, CDCl₃): δ = -0.08 (s, 6H), 0.80 (s, 9H), 1.04 (t, 3H), 2.00 (t, 1H), 2.75 (q, 2H), 4.00 (t, 2H), 4.18 (t, 2H), 4.60 (d, 2H), 6.84 (s, 2H), 7.02 (s, 1H).

LRMS (thermospray): m/z [MH⁺] 461.

Preparation 39

15 {1-(2-{{[tert-Butyl(dimethyl)silyl]oxy}ethyl)-4-[(3,5-dichlorophenyl)sulfanyl]-5-ethyl-1*H*-pyrazol-3-yl}acetonitrile



To a stirred solution of the alcohol, (340mg, 0.74mmol) of Preparation 38 in dichloromethane (6ml) was added triethylamine (113 μ l, 0.81mmol) and methanesulfonyl chloride (63 μ l, 0.81mmol). After 1 hour at room temperature the reaction mixture was partitioned between dichloromethane and water and then the aqueous phase was further extracted with dichloromethane. The combined organic phases were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give a colourless oil. This crude mesylate was dissolved in dimethylformamide (5ml) and sodium cyanide (109mg, 2.22mmol) was added. The reaction mixture was heated at 60°C for 1 hour. After cooling to room temperature, the mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane and water. The organic phase was separated, washed with water and brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give a yellow oil. The crude product was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (3:1, by volume) to afford the title compound (240mg) as a colourless oil.

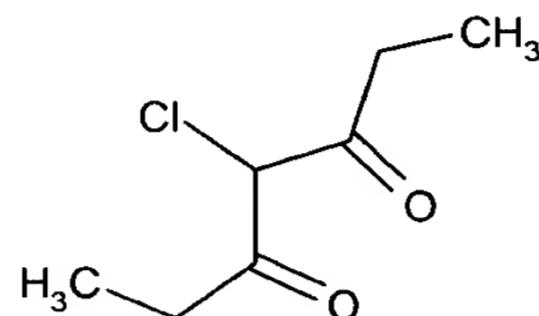
¹H-NMR (400MHz, CDCl₃): δ = -0.04 (s, 6H), 0.82 (s, 9H), 1.11 (t, 3H), 2.78 (q, 2H), 3.62 (s, 2H), 4.02 (t, 2H), 4.20 (t, 2H), 6.82 (s, 2H), 7.10 (s, 1H).

LRMS (electrospray): m/z [M+Na⁺] 492.

5 Accurate Mass: Found: 470.1250 [MH⁺]; C₂₁H₃₀Cl₂N₃OSSi requires 470.1250 [MH⁺].

Preparation 40

4-Chloro-3,5-heptanedione



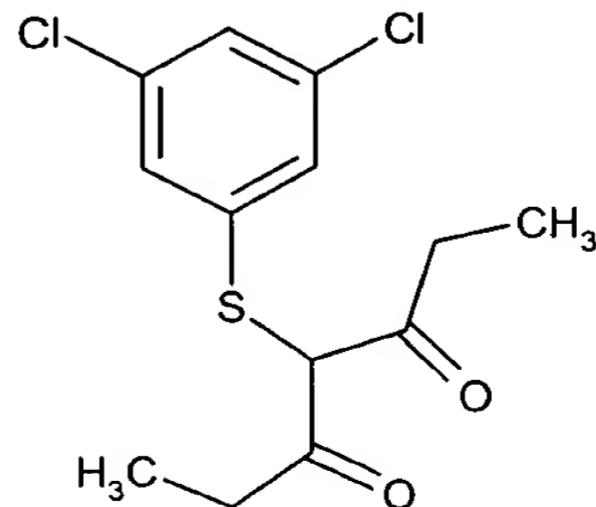
Chlorotrimethylsilane (29.7ml, 0.234mol) was added dropwise to a stirred pale yellow
10 solution of tetrabutylammonium bromide (1.26g, 3.9mmol) in dry acetonitrile (116ml) at room temperature under nitrogen. The resulting solution was cooled in ice and 3,5-heptanedione (10.6ml, 78.0mmol) and then dry dimethylsulphoxide (16.6ml, 0.234mol) were added dropwise over 5 minutes producing a yellow solution which was allowed to warm slowly to room temperature, with stirring, over 4 hours. The mixture was diluted with water (1litre),
15 stirred for 10min and then extracted with ether (1x500ml, 2x250ml). The combined ether layers were dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a yellow oil. The crude product was purified by distillation under reduced pressure to afford the title compound (5.5g) as a pale yellow oil, b.p. 102-105°C/54mmHg containing ca. 10% 4,4-dichloro-3,5-heptanedione as estimated by microanalysis.

20 ¹H-NMR (400MHz, CDCl₃): δ = 1.12 (t, 6H), 2.59 (q, 4H), 4.77 (s, 0.2H, diketone), 15.50 (s, 0.8H, enol).

LRMS (thermospray): m/z [MNH₄⁺] 180 for title compound and 214 for dichlorinated impurity.

Preparation 41

25 4-[(3,5-Dichlorophenyl)sulfanyl]-3,5-heptanedione



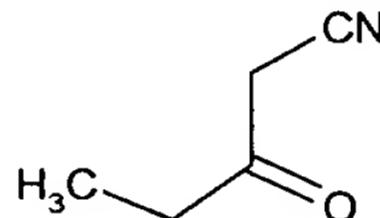
To a stirred solution of the chlorodiketone (1.0g) of Preparation 40 in acetone (30ml) was added 3,5-dichlorothiophenol (1.1g, 6.15mmol), potassium carbonate (900mg, 6.77mmol) and sodium iodide (900mg, 6.15mmol). After 18 hours the reaction mixture was diluted with water (20ml) and the acetone was removed under reduced pressure. The residue
5 was partitioned between 2M HCl and dichloromethane. The aqueous phase was separated and further extracted with dichloromethane. The combined organic phases were washed with brine, dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a yellow oil (2g). The crude product was used without further purification.

10 $^1\text{H-NMR}$ (400MHz, CDCl_3): enol tautomer, δ = 1.03 (t, 6H), 2.62 (m, 4H), 6.91 (s, 2H),
7.08 (s, 1H).

LRMS (electrospray): m/z [M-H⁺] 303.

Preparation 42

3-Oxopentanenitrile

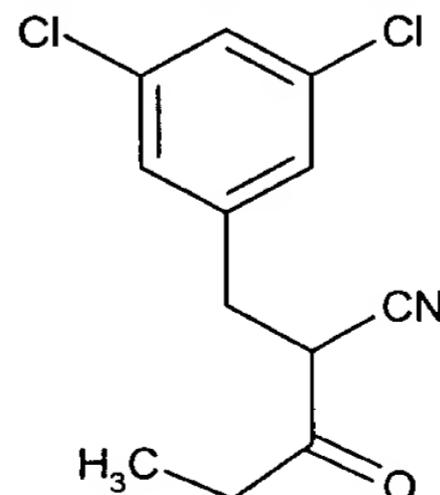


15 A mixture of ethyl propionate (20g, 196mmol) and sodium ethoxide (13.3g, 196mmol) was heated at 80°C. After 15 mins acetonitrile (13.3ml, 255mmol) was added and the mixture was heated at 120°C. After 13 hours the reaction mixture was cooled and acidified to pH2 using 1M HCl. The volatile reaction components were removed under reduced pressure and the mixture was extracted using dichloromethane. The organic phase was separated,
20 washed with water, washed with brine and concentrated under reduced pressure to give a brown oil (10g). The crude product was used without further purification.

$^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 1.01 (t, 3H), 2.56 (q, 2H), 3.43 (s, 2H).

Preparation 43

2-(3,5-Dichlorobenzyl)-3-oxopentanenitrile



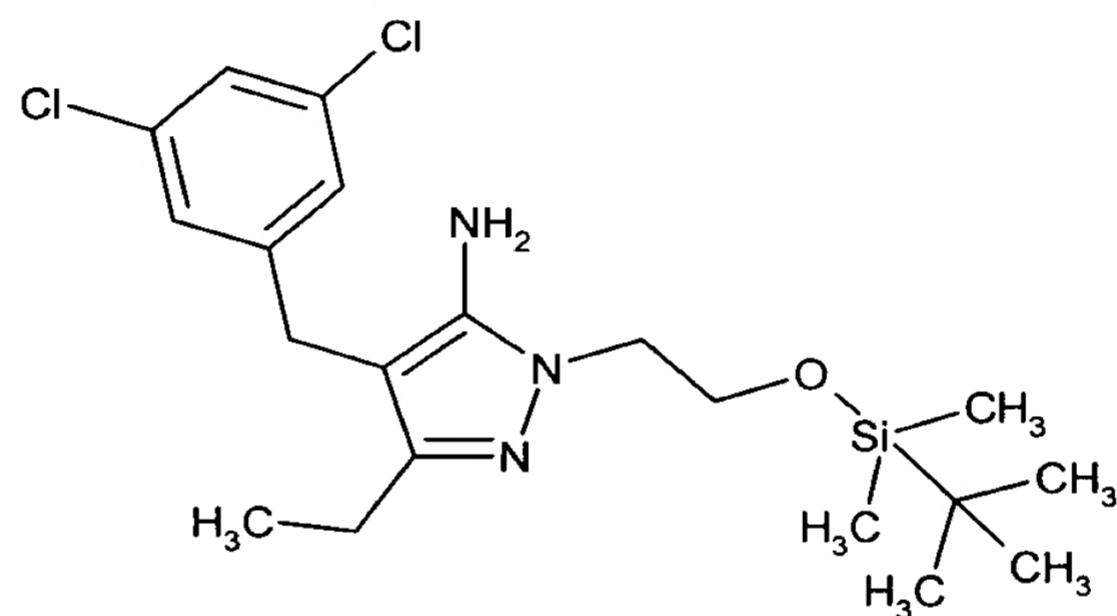
25 A stirred solution of the nitrile (11.3g, 117mmol) of Preparation 42 and 3,5-dichlorobenzylchloride (27.8g, 117mmol) in N, N-dimethylformamide (200ml) was cooled to 0°C before addition of sodium hydride (60% w/w suspension in mineral oil) (9.3g, 234mmol) portionwise. After 2 hours the reaction mixture was quenched by the addition of saturated

aqueous ammonium chloride solution (500ml) and the resulting mixture was extracted with ethyl acetate. The organic phase was separated and twice washed with water, washed with brine, dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a dark oil. The crude product was purified by flash chromatography on silica gel eluting 5 with cyclohexane:ethyl acetate (9:1, by volume) to afford the title compound (7g) as a white solid, m.p. 59-60°C.

10 $^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 1.04 (t, 3H), 2.68 (m, 2H), 3.02 (m, 1H), 3.18 (m, 1H), 3.58 (m, 1H), 7.10 (s, 2H), 7.25 (s, 1H).
LRMS (thermospray): m/z [M+NH₄⁺] 273.
Microanalysis: Found: C, 56.06; H, 4.33; N, 5.41. $\text{C}_{12}\text{H}_{11}\text{Cl}_2\text{NO}$ requires C, 56.27; H, 4.33; N, 5.47%.

Preparation 44

1-(2-{{[tert-Butyl(dimethyl)silyl]oxy}ethyl)-4-(3,5-dichlorobenzyl}-3-ethyl-1*H*-pyrazol-5-amine



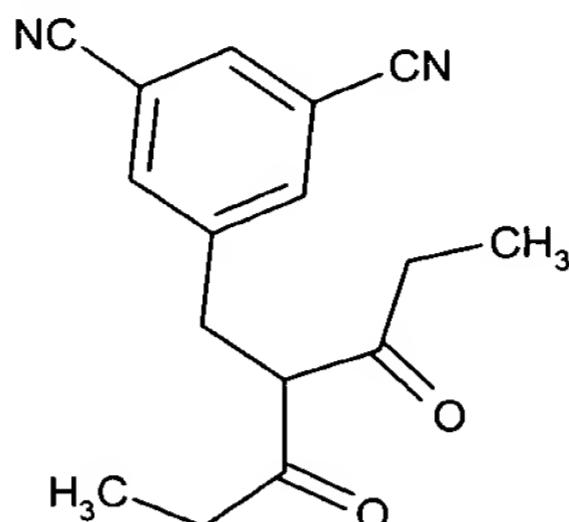
15 To a solution of the pyrazole of Example 89 (3.0g, 9.6mmol) in dimethylformamide (20ml) was added imidazole (850mg, 12.5mmol), followed by tert-butyldimethylchlorosilane (1.58g, 10.6mmol). The solution was stirred at room temperature for 20 hours. The reaction mixture was partitioned between diethyl ether and aqueous sodium carbonate and the aqueous phase was separated and further extracted with diethyl ether. The combined 20 organic phases were washed with water, washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:5:0.5, by volume) to afford the title compound (4.0g) as a colourless oil.

25 $^1\text{H-NMR}$ (400MHz, CDCl_3): δ = -0.08 (s, 6H), 0.79 (s, 9H), 1.11 (t, 3H), 2.42 (q, 2H), 3.58 (s, 2H), 3.63 (s, 2H), 3.87 (t, 2H), 4.07 (t, 2H), 7.00 (s, 2H), 7.14 (s, 1H).

LRMS (thermospray): m/z [MH⁺] 428.
Microanalysis: Found: C, 55.92; H, 7.28; N, 9.74. $\text{C}_{20}\text{H}_{31}\text{Cl}_2\text{N}_3\text{OSi}$ requires C, 56.06; H, 7.29; N, 9.81%.

Preparation 45

5-(3-Oxo-2-propionylpentyl)isophthalonitrile



Sodium hydride (60% dispersion in oil, 116mg, 2.90mmol) was added to a stirred
5 solution of 3,5-heptanedione (358 μ l, 2.64mmol) in 2-butanone (5ml) at room temperature
under nitrogen. After evolution of hydrogen had ceased, sodium iodide (396mg, 2.64mmol)
and then a solution of 5-bromomethyl-isophthalonitrile (J.Org.Chem., 1990, 55 (3), 1040-
1043) (584mg, 2.64mmol) in 2-butanone (6ml) was added and the mixture was heated at
reflux for 6 hours. After cooling, the mixture was quenched with water (1ml) and the 2-
10 butanone was removed under reduced pressure. The residue was partitioned between water
(40ml) and dichloromethane (40ml) and the organic layer was separated, dried over
magnesium sulphate, filtered and concentrated under reduced pressure. The crude product
was purified by flash chromatography on silica gel eluting with a solvent gradient starting with
15 pentane:ethyl acetate (10:1, by volume) and finishing with pentane:ethyl acetate (3:1, by
volume) to give the title compound (370mg) as a white solid m.p. 67-69°C.

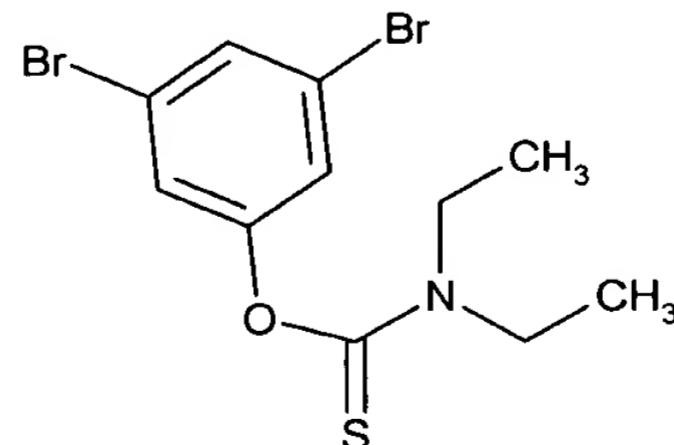
$^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 1.1 (6H, m), 2.44 (4H, m), 3.20 (2H, d, keto), 3.79 (2H,
s, enol), 3.98 (1H, t, keto), 7.61 (2H, s), 7.8 (1H, s), 17.11 (1H, s, enol).

LRMS (electrospray): m/z [M-H $^+$] 267.

Microanalysis: Found: C, 71.35; H, 6.02; N, 10.41. $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$ requires C, 71.62; H,
20 6.01; N, 10.44%.

Preparation 46

O-(3,5-Dibromophenyl) diethylthiocarbamate



A solution of 3,5-dibromophenol (prepared according to Recl. Trav. Chim. Pays-Bas.
25 1908, 27, 30) (10.08g, 40mmol) and diethylthiocarbamyl chloride (7.9g, 52 mmol) in 1-methyl-
2-pyrrolidinone (80ml) was cooled to 0°C under an atmosphere of nitrogen. Sodium hydride

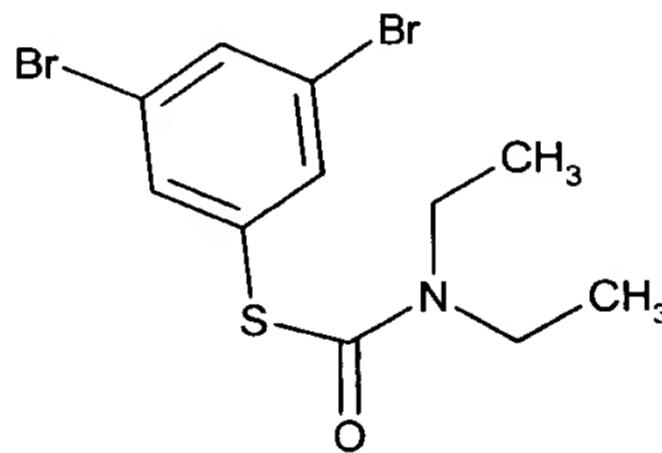
(60% dispersion in mineral oil, 1.92g, 48 mmol) was added portionwise with stirring. The mixture was allowed to warm to 20°C and stirred under nitrogen for two hours. The mixture was partitioned between diethyl ether (250ml) and water (350ml) and the aqueous layer was further extracted with diethyl ether (250ml then 100ml). The organic layers were combined, 5 washed with water (150ml) and brine (150ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a yellow solid. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:pentane (1:1, by volume) to provide the title compound (13.4g) as a white solid, m.p. 72-74°C.

10 $^1\text{H-NMR}$ (400MHz, CDCl_3): δ = 1.27 (m, 6H), 3.62 (q, 2H), 3.84 (q, 2H), 7.17 (d, 2H), 7.51 (d, 1H).

Microanalysis: Found: C, 35.99; H, 3.54; N, 3.73. $\text{C}_{11}\text{H}_{13}\text{Br}_2\text{NOS}$ requires C, 35.99; H, 3.57; N, 3.82%.

Preparation 47

S-(3,5-dibromophenyl) diethylthiocarbamate



15

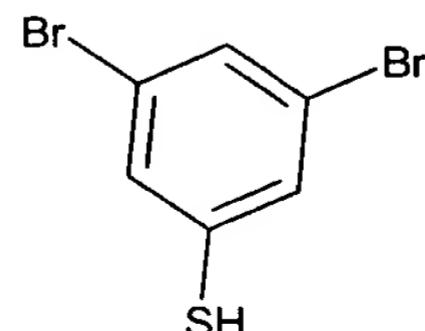
O-(3,5-dibromophenyl) diethylthiocarbamate (13.24g, 36.1 mmol) (Preparation 46) was heated to 200°C, with stirring, under an atmosphere of nitrogen, for 15 hours to leave a yellow oil. A sample of this material (1g) was purified by flash chromatography on silica gel eluting with pentane:dichloromethane (1:1, by volume) to provide the title compound (700mg) 20 as a colourless oil.

16 $^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 1.26 (m, 6H), 3.43 (q, 4H), 7.62 (s, 2H), 7.68 (s, 1H).

Microanalysis: Found: C, 35.92; H, 3.47; N, 3.69. $\text{C}_{11}\text{H}_{13}\text{Br}_2\text{NOS}$ requires C, 35.99; H, 3.57; N, 3.82%.

Preparation 48

3,5-Dibromobzenethiol



25

Sodium hydroxide (1.96g, 49mmol) was added to a solution of S-(3,5-dibromophenyl) diethylthiocarbamate (12g, 32.7mmol) (Preparation 47) in methanol (33ml) and the mixture

was heated at reflux for 15 hours. The mixture was cooled to 20°C and concentrated under reduced pressure. The residue was partitioned between dichloromethane (90ml) and water (250ml) and the aqueous layer was further extracted with dichloromethane (90ml). The combined organic layers were washed with a solution of sodium hydroxide (1N, 100ml). The 5 combined aqueous layers were cooled to 0°C and the pH was adjusted to 2 by the addition of concentrated hydrochloric acid, giving a white suspension. This suspension was extracted with dichloromethane (2x250ml) and the combined extracts were washed with brine (25ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave the title compound as a yellow solid (6.7g).

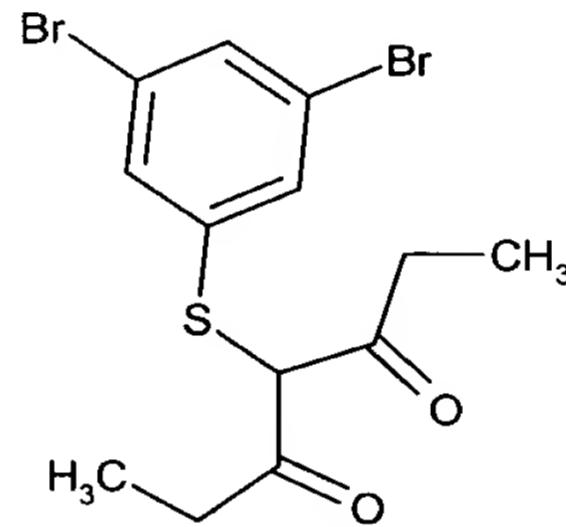
10 ¹H-NMR (300MHz, CDCl₃): δ = 3.55 (s, 1H), 7.36 (m, 2H), 7.46 (s, 1H).

LRMS (electrospray): m/z [M-H] 267.

Microanalysis: Found: C, 27.01; H, 1.42. C₆H₄Br₂S requires C, 26.89; H, 1.50%.

Preparation 49

4-[(3,5-Dibromophenyl)sulfanyl]-3,5-heptanedione



15 Potassium carbonate (1.9g, 14mmol) was added to a solution of 3,5-dibromobzenethiol (2.84g, 10.5mmol) (Preparation 48) and 4-chloroheptane-3,5-dione (1.7g, 10.5mmol) (Preparation 40) in acetone (12ml) producing a white suspension. The mixture was stirred at room temperature for 15 hours. The mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (100ml) and 1N hydrochloric acid (70ml). The aqueous layer was extracted with further dichloromethane (2x100ml). The combined organic layers were washed with brine (50ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a pink oil. The crude product was purified by flash chromatography on silica gel eluting with pentane:dichloromethane (1:1, by volume) to provide the title compound (3g) as a pink oil.

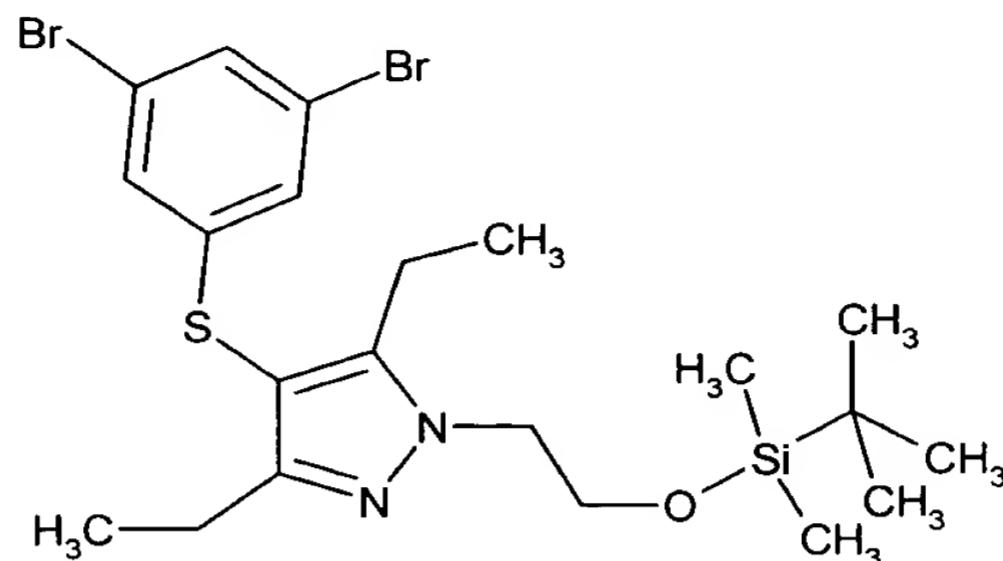
20 ¹H-NMR (300MHz, CDCl₃): δ = 1.13 (m, 6H), 2.7 (m, 4H), 7.12 (s, 2H), 7.42 (s, 1H), 17.70 (s, 1H).

LRMS (thermospray): m/z [MNH₄⁺] 412.

LRMS (electrospray): m/z [M-H] 393.

Preparation 50

1-(2-{{[tert-Butyl(dimethyl)silyl]oxy}ethyl}-4-[(3,5-dibromophenyl)sulfanyl]-3,5-diethyl-1*H*-pyrazole

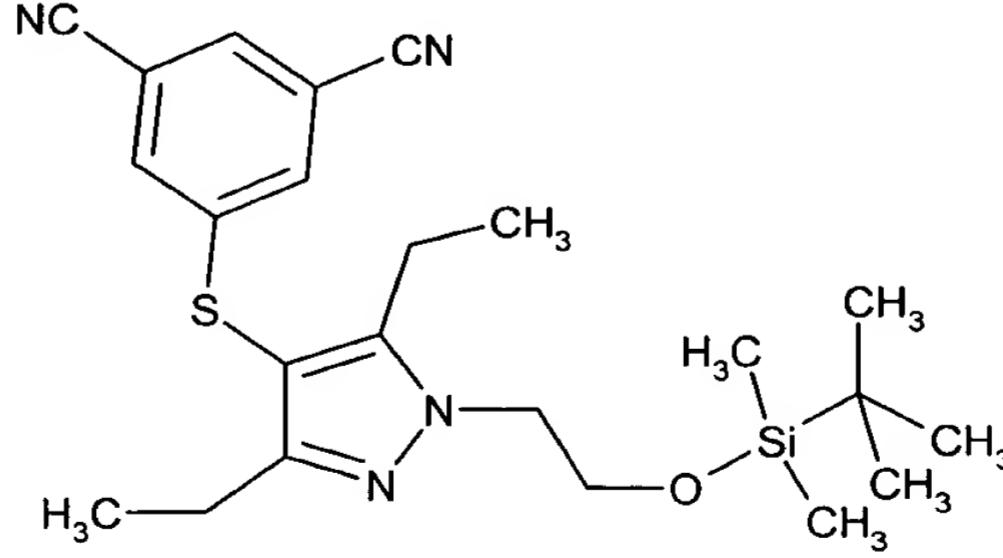


5 A solution of 2-{4-[(3,5-dibromophenyl)sulfanyl]-3,5-diethyl-1*H*-pyrazol-1-yl}ethanol (1.3g, 3mmol) (Example 93) in dimethylformamide (3ml) was treated with imidazole (270mg, 4mmol) and *tert*-butyl(chloro)dimethylsilane (500mg, 3.3mmol) and stirred at 20°C for 15 hours. The mixture was partitioned between diethyl ether (70ml) and citric acid solution (5% weight:volume in water, 150ml). The aqueous layer was further extracted with diethyl ether 10 (70ml) and the combined organic layers were washed with brine (2x70ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with pentane:dichloromethane (1:1, by volume) to provide the title compound (1.2g) as a colourless oil.

15 ¹H-NMR (300MHz, CDCl₃): δ = -0.05 (s, 6H), 0.84 (s, 9H), 1.10 (t, 3H), 1.19 (t, 3H), 2.58 (q, 2H), 2.75 (q, 2H), 4.04 (m, 2H), 4.18 (m, 2H), 7.05 (s, 2H), 7.35 (s, 1H).
LRMS (electrospray): m/z [MH⁺] 549.

Preparation 51

5-{{[1-(2-{{[tert-Butyl(dimethyl)silyl]oxy}ethyl}-3,5-diethyl-1*H*-pyrazol-4-yl]sulfanyl}isophthalonitrile



20

A solution of 1-(2-{{[tert-butyl(dimethyl)silyl]oxy}ethyl}-4-[(3,5-dibromophenyl)sulfanyl]-3,5-diethyl-1*H*-pyrazole (500mg, 0.9mmol) (Preparation 50) in dimethylformamide (2ml) was treated with zinc cyanide (130mg, 1.1mmol), 1,1'-bis(diphenylphosphino)ferrocene (65mg, 0.12mmol) and tris(dibenzylideneacetone)dipalladium (92mg, 0.1mmol) and the resulting

brown suspension was heated at 100°C for 2¹/₂ days. After cooling the mixture was diluted with water (70ml) and extracted with ethyl acetate (2x60ml). The combined organic layers were washed with water (20ml) and brine (30ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a brown oil. The crude product was purified by
5 flash chromatography on silica gel eluting with pentane:dichloromethane (1:1, by volume) then dichloromethane and finally with dichloromethane:ethyl acetate (19:1, by volume) to provide the title compound (180mg) as a brown oil.

¹H-NMR (300MHz, CDCl₃): δ = -0.03 (s, 6H), 0.84 (s, 9H), 1.10 (t, 3H), 1.18 (t, 3H), 2.56 (q, 2H), 2.72 (q, 2H), 4.06 (m, 2H), 4.20 (m, 2H), 7.43 (s, 2H), 7.60 (s, 1H).

10 LRMS (thermospray): m/z [MH⁺] 441.

PHARMACOLOGICAL ACTIVITY

All the compounds of the Examples were tested for their ability to inhibit HIV-1 reverse transcriptase by the method described on page 36 and all had an IC₅₀ of less than 100 micromolar.

RECORDED BY: J. M. HARRIS
DATE: 10/10/02